GI Epithelial Cancers

Acknowledgment and Disclaimer
MEDICINE THROUGH THE GLASS SLIDE
is a free educational platform, an offering shaped by personal experience, informed by scientific literature and enriched by publicly available knowledge.

We walk in the light cast by giants, visionaries whose tireless pursuit of truth has illuminated the intricate beauty of medicine and microscopy.

This work pays homage to the researchers clinicians and educators whose insights form the bedrock of our understanding. Each image, each reflection echoes their enduring legacy.
All sources are acknowledged with gratitude and intellectual contributions are credited with full respect for legal and ethical standards.

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GI Cancers

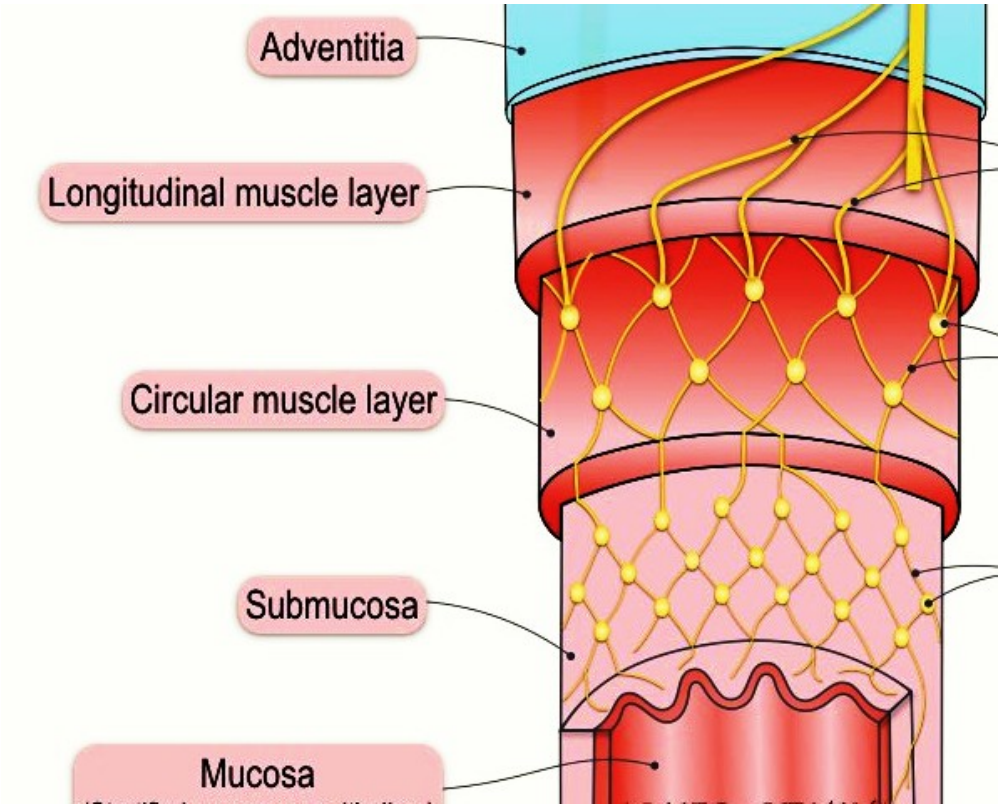
GI walls have **4 layer** and **many type of tissues**

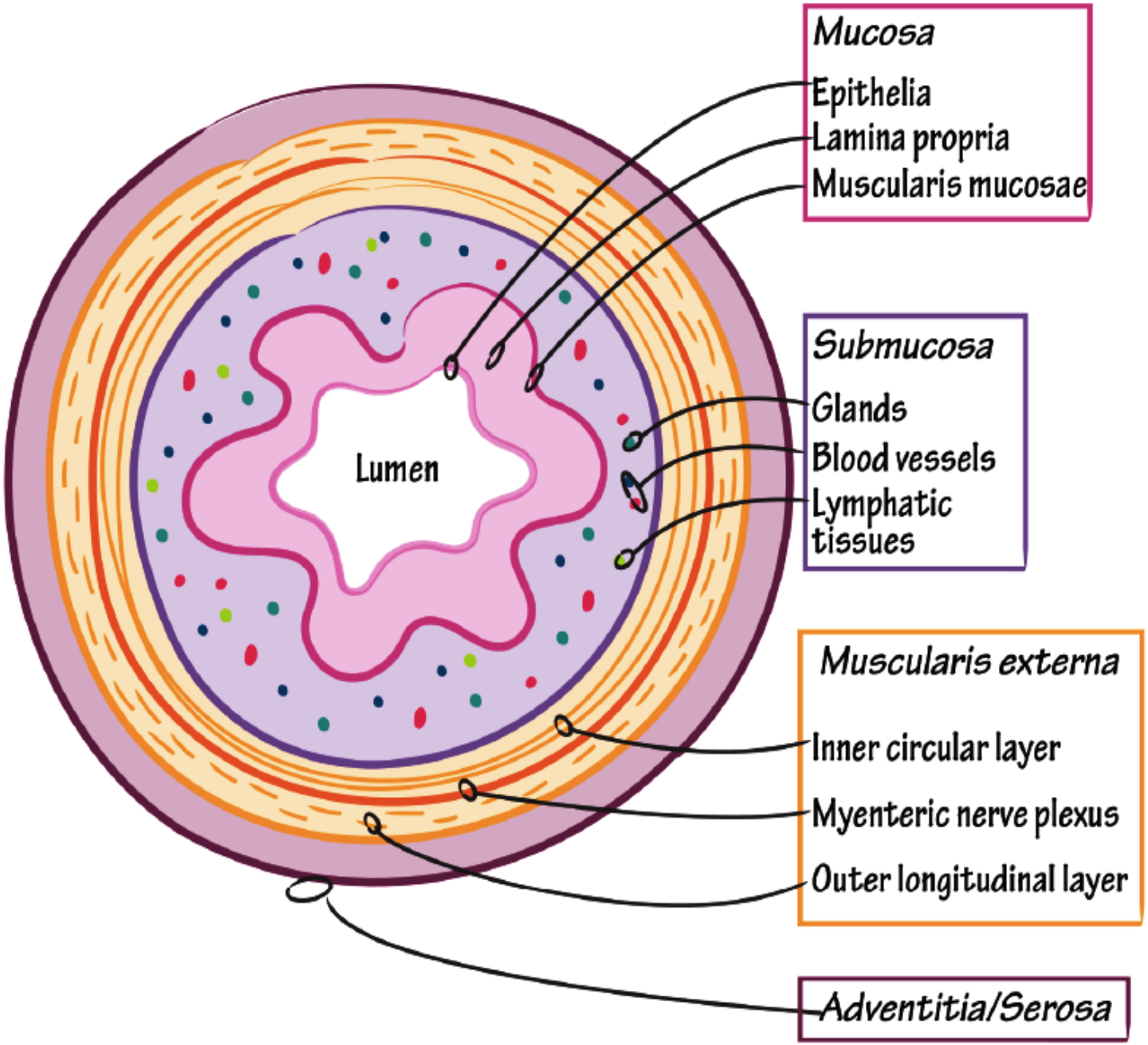
Almost all GI cancers arise from the **lining epithelium**

Almost all are **carcinomas**

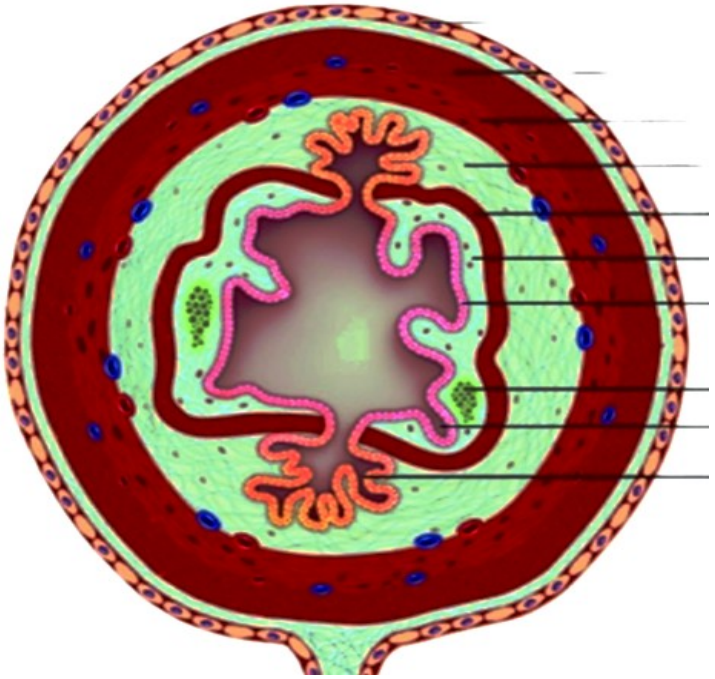
Neuroendocrine tumors also occur in the mucosa

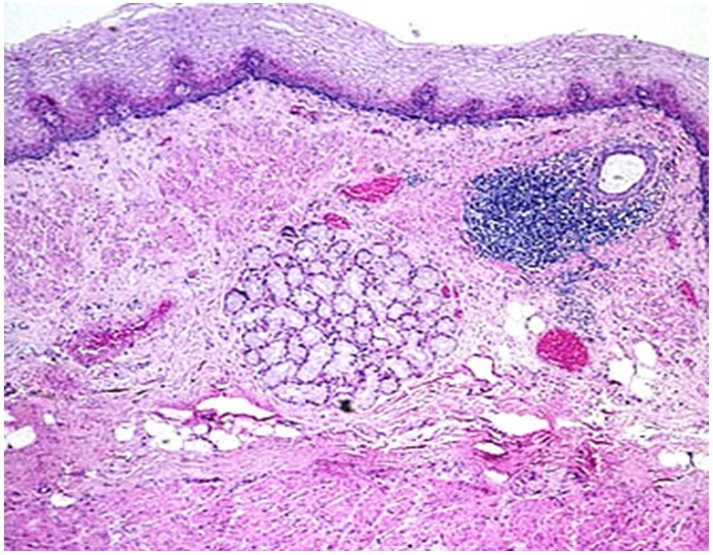
Non-epithelial tumours (GIST, lymphoma, etc) are infrequent




Mucosa
Epithelia
Lamina propria
Muscularis mucosae
Submucosa
Glands
Blood vessels
Lymphatic tissues
Lumen
Muscularis externa
Inner circular layer
Myenteric nerve plexus
Outer longitudinal layer
Adventitia/Serosa

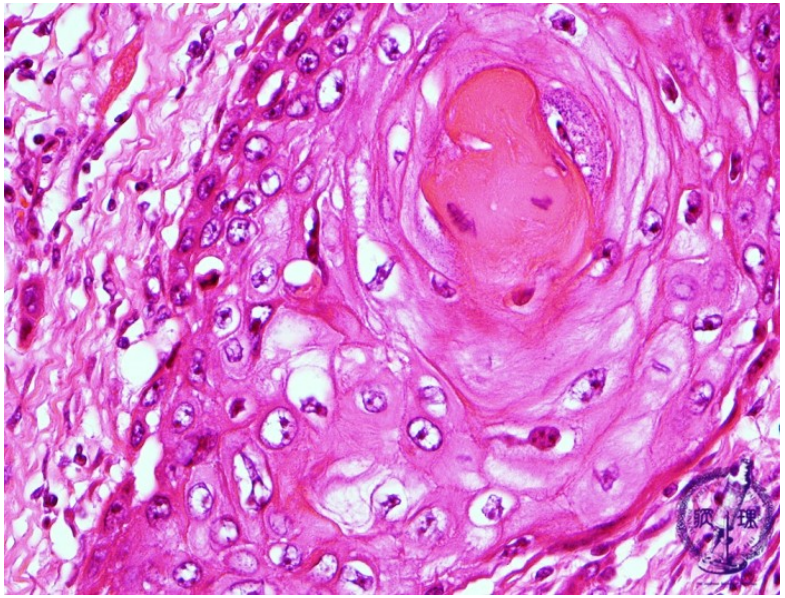
Normal esophagus

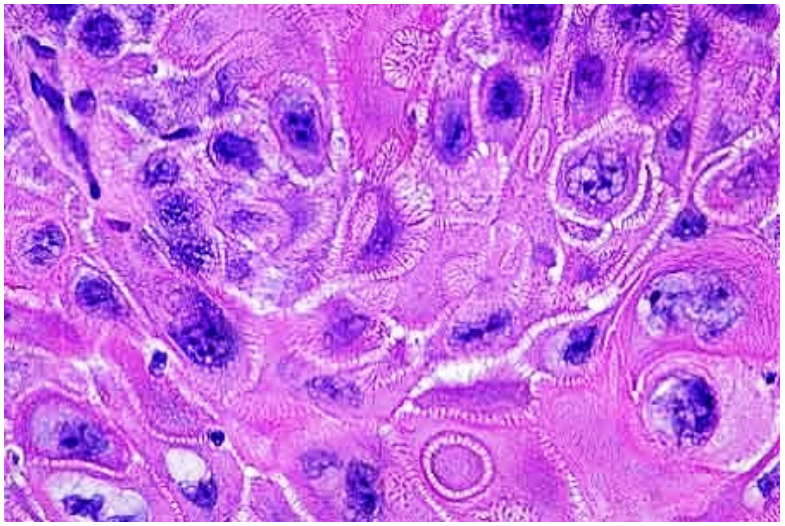




Malignant epithelial tumors of the esophagus
Squamous cell carcinoma
Adenocarcinoma
Adenosquamous carcinoma
Undifferentiated carcinoma
Salivary glad carcinomas Adenoid cystic carcinoma Mucoepidermoid carcinoma
Neuroendocrine Neoplasms (NEN) Neuroendocrine Tumors (NET) Neuroendocrine Carcinomas (NEC)

Epithelial tumors of the esophagus		
Carcinoma >95% Globally, **~80%** are squamous cell carcinomas and **~20%** are adenocarcinomas In the USA, **~20%** are squamous cell carcinomas and **~80%** are adenocarcinoma	Adenocarcinoma NOS	Tubular, papillary, mucinous, signet-ring cell patterns and other types
	Squamous cell carcinoma NOS	Verrucous SCC Spindle cell SCC Basaloid SCC
	Adenosquamous carcinoma Undifferentiated carcinoma	
	Salivary glad carcinomas	Adenoid cystic carcinoma Mucoepidermoid carcinoma
Neuroendocrine Neoplasm (NEN) <1%	Neuroendocrine Tumor (NET)	Carcinoid tumor
	Neuroendocrine Carcinoma (NEC)	Small cell NEC Large cell NEC
Mixed	Mixed neuroendocrine-non-neuroendocrine (MiNEN)	NEC ad SCC NEC and adenocarcinoma





Squamous cell carcinoma (SCC)

Malignant cells that **produce keratin and have intercellular bridges**

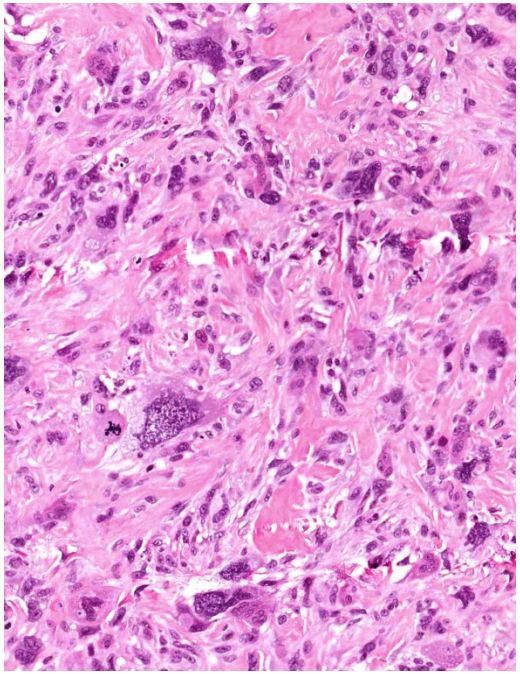
Nests or islands with **variable degrees of keratinization,** usually abundant nest forming in well differentiated SCCs to no keratinization in poorly differentiated SCCs)

Squamous cell carcinoma variants

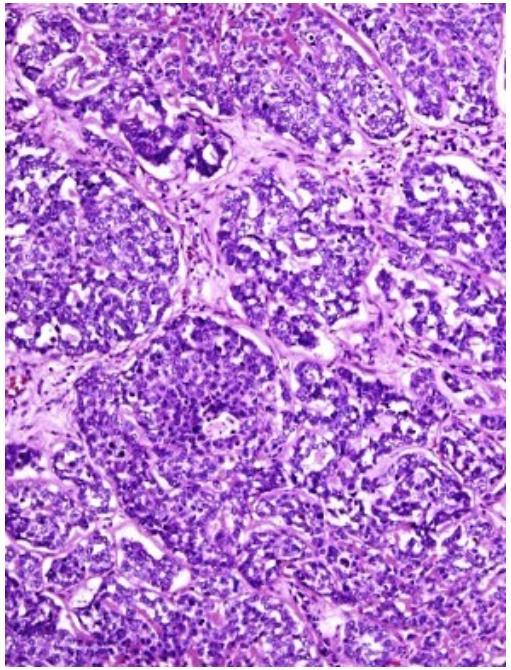
- Verrucous squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Basaloid squamous cell carcinoma

Verrucous SCC

Favorable



Spindle cell SCC

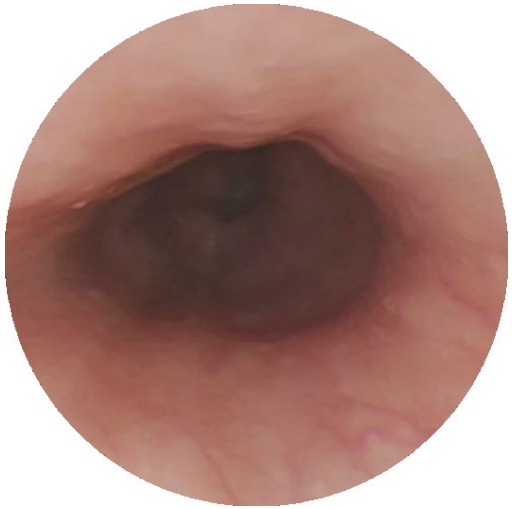


Basaloid SCC

Unfavorable

SCC of the esophagus	
Incidence	Much more common in **underdeveloped areas** of certain countries than in Western countries Highest incidence regions are **Asia, South American and Sothern Africa** **Incidence can vary by a 100-fold** between and within regions and countries
Risk factors	Risk factors include **alcohol and tobacco, nutritional deficiencies and exposure to carcinogens** (polycyclic hydrocarbons, nitrosamines, etc)
SCC of the esophagus in the **US** is most frequent in **male African Americans** with male to female ratio of 4:1	

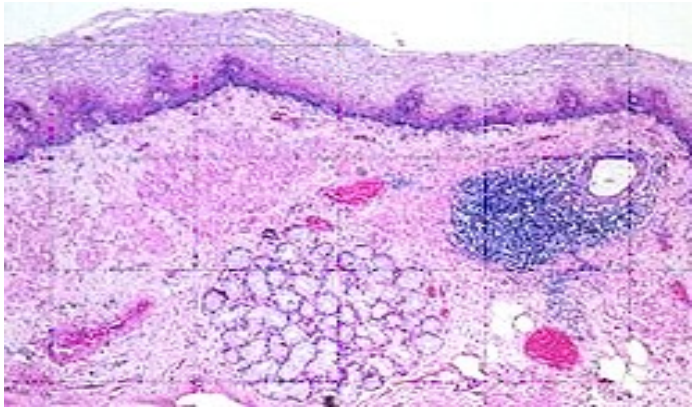
Evolution of SCC of the esophagus



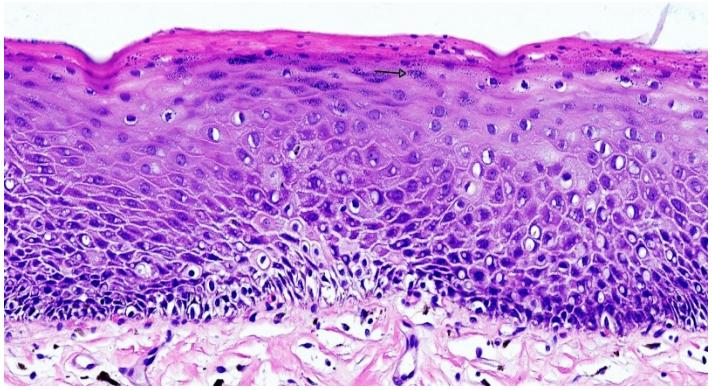
Normal

Dysplasia

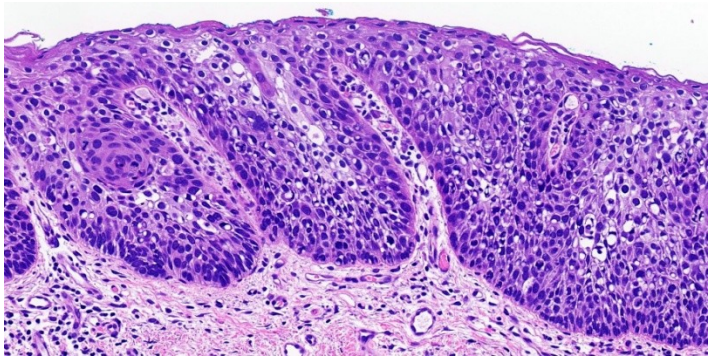
Normal



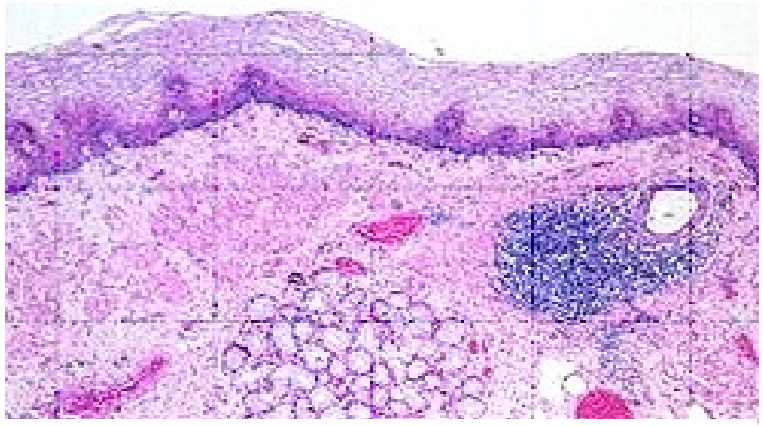
Dysplasia, LG



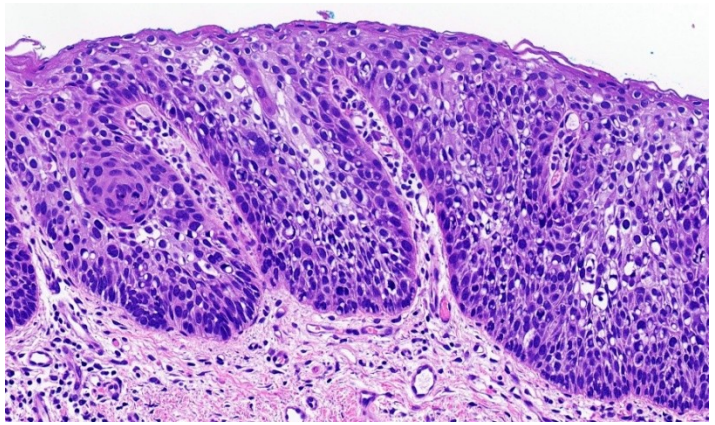
Dysplasia, HG



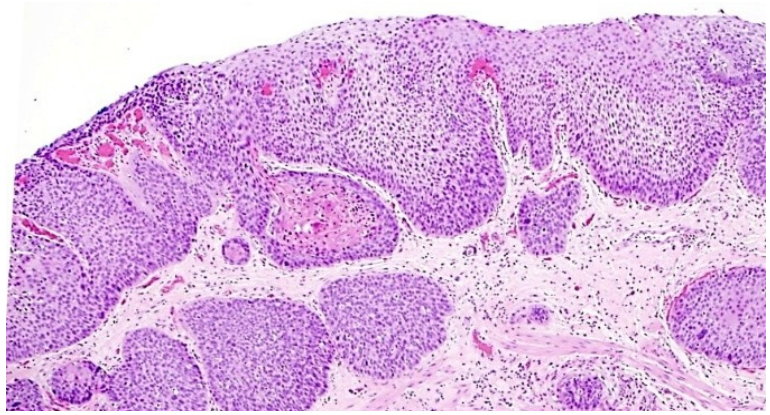
Pathway to squamous carcinoma in the esophagus



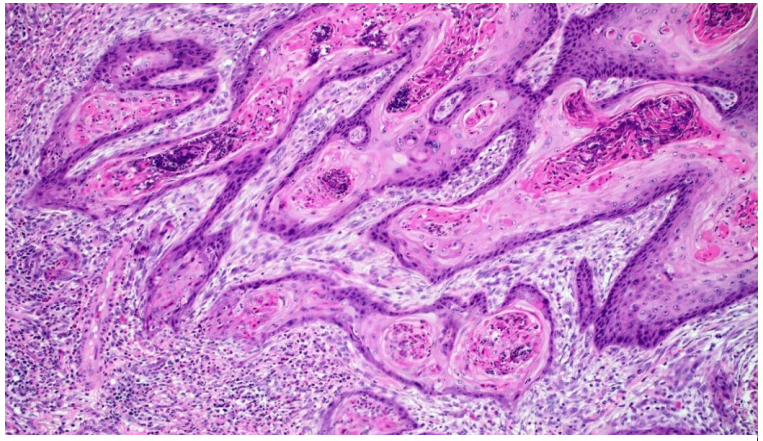
Normal squamous mucosa



Squamous dysplasia



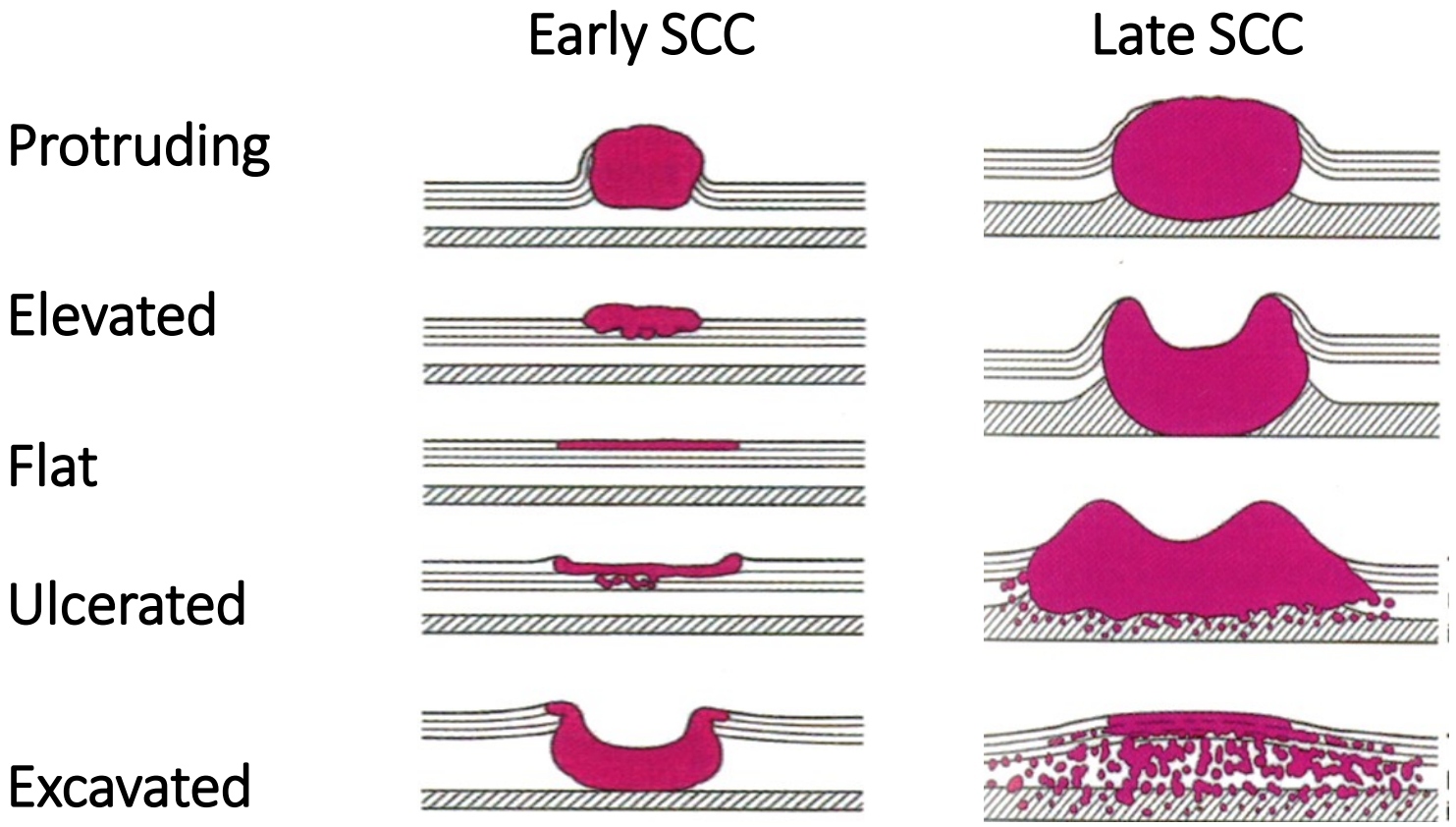
Early invasive SCC



Invasive SCC

Superficial squamous cell carcinoma of the esophagus

- Cancer confined to mucosa and submucosa regardless of nodal status
- First recognized in screening programs in **China and Japan**
- Currently accounts for up to **25%** of resected esophageal squamous cell carcinomas in the US and Western Europe

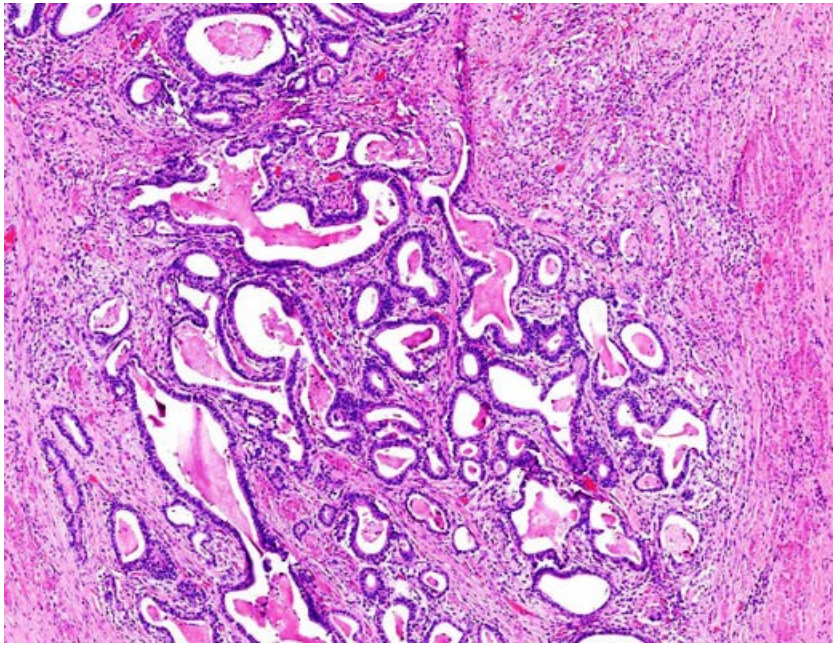


Adenocarcinoma of the esophagus

Gland forming or mucin producing cancer

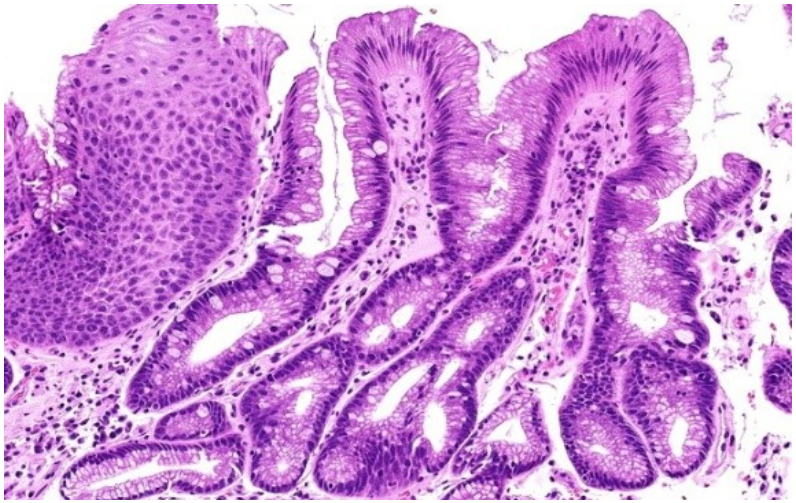
Adenocarcinoma is **more common than squamous cell carcinoma** and makes up about **80%** of esophageal cancer cases

Arises in Barrett esophagus

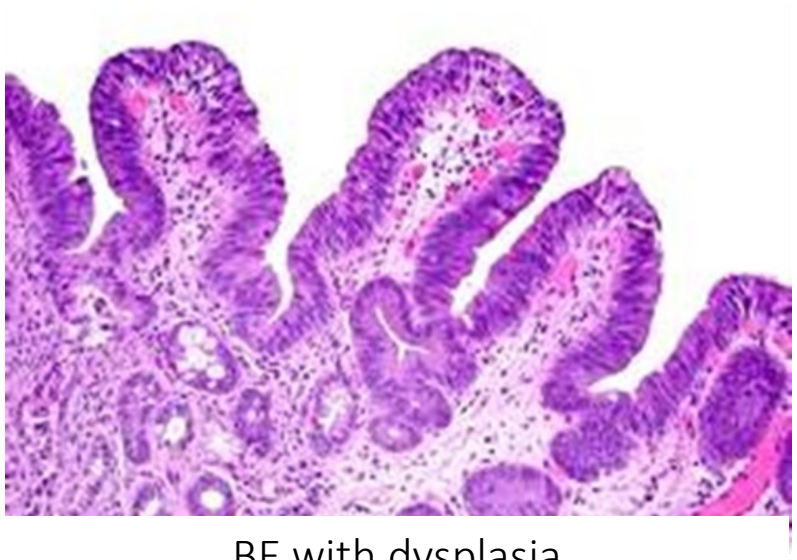


Adenocarcinoma of the esophagus	
Incidence	More common in **western countries** than in underdeveloped regions **Incidence** in western countries has increased 10 folds since 1970
Risk factors	Arises in a background of **GERD and Barrett esophagus** **Dysplasia in Barrett esophagus, smoking, obesity**
Most frequent in **white American males** with male to female ration of 7:1	

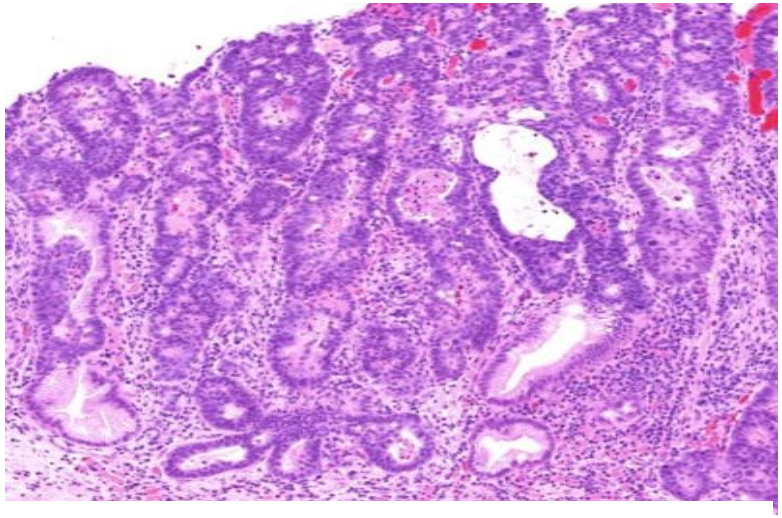
Pathway to adenocarcinoma in the esophagus



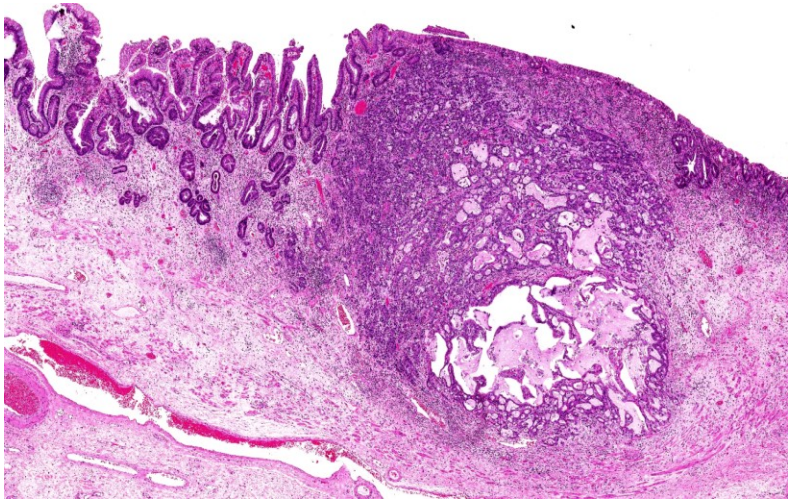
BE, no dysplasia



BE with dysplasia

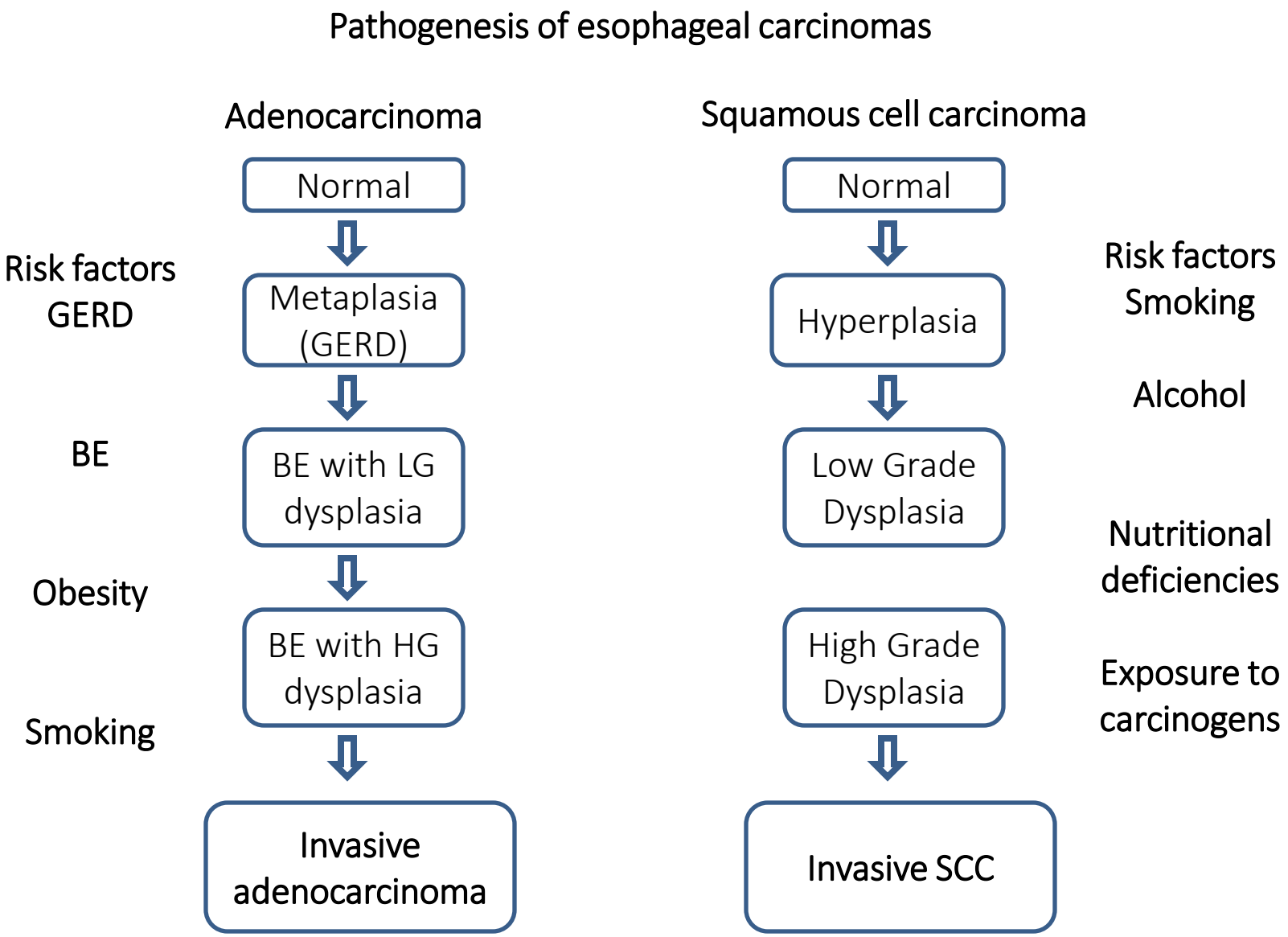


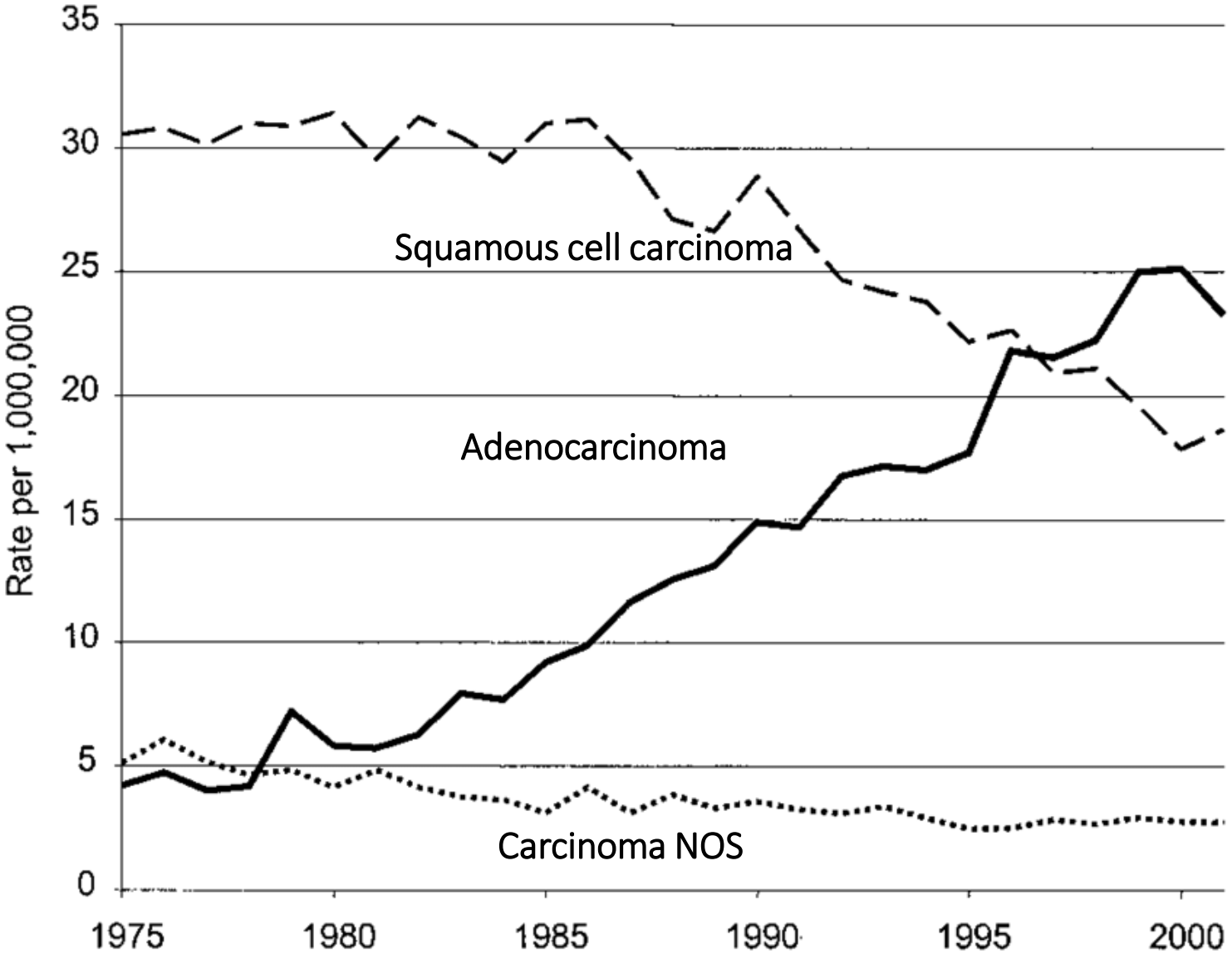
BE with adenocarcinoma



BE with dysplasia and adenocarcinoma

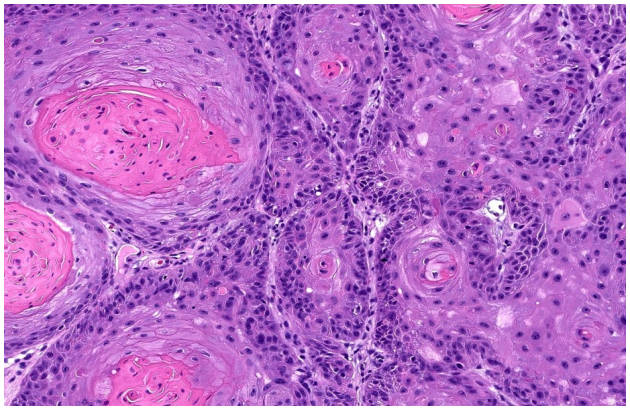
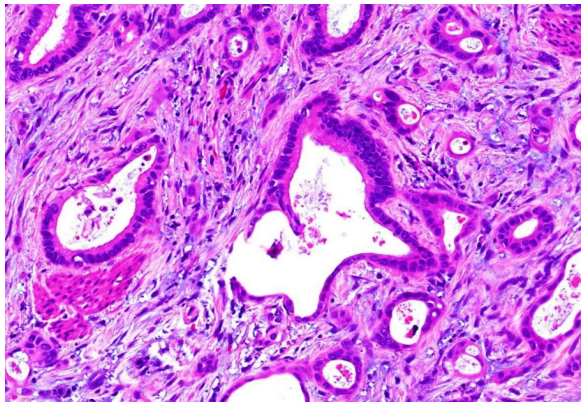
Esophageal carcinomas		
Type	**Squamous cell carcinoma**	**Adenocarcinoma NOS**
Risk Factor	Smoking, alcohol Nutritional deficiencies Exposure to carcinogens	GERD Barrett esophagus Obesity, smoking
Epidemiology	Common in Asia, Africa, South America	Common in Western countries
Age & sex (USA)	Middle age or older males **African Americans**	Middle age or older males **White Americans**
Symptoms	Dysphagia, odynophagia, obstruction, vomiting, weight loss (cachexia), hemorrhage and sepsis (fistula)	
Location	Mostly in the middle (55%) and lower esophagus (35%)	Lower esophagus (>80%)
Survival	10% overall (75% early in early cancer)	25% overall (80% in early cancer)

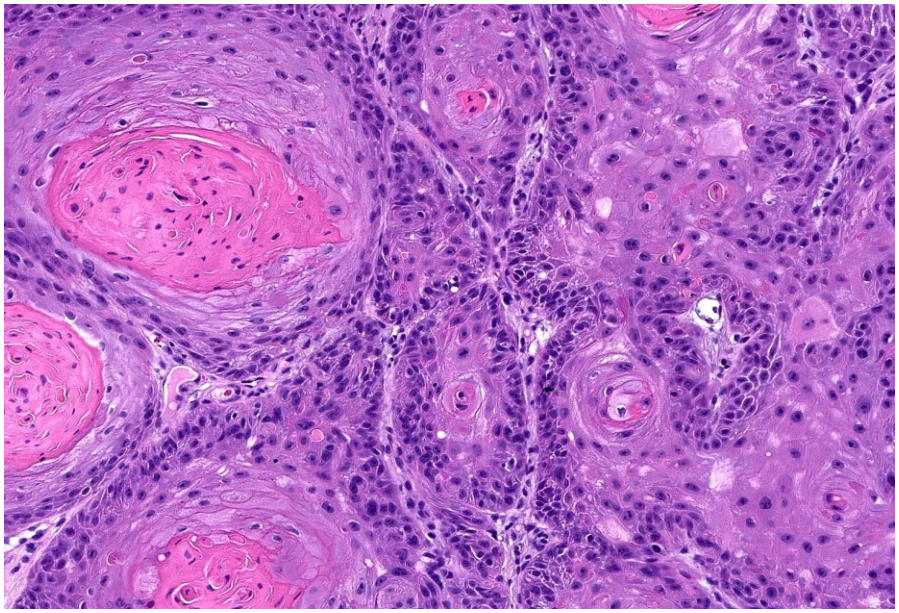

Pathogenesis of esophageal carcinomas
Adenocarcinoma
Squamous cell carcinoma
Normal
Metaplasia (GERD)
BE with LG dysplasia
BE with HG dysplasia
Invasive adenocarcinoma
Normal
Hyperplasia
Low Grade Dysplasia
High Grade Dysplasia
Invasive SCC
Risk factors GERD
BE
Obesity
Smoking
Risk factors Smoking
Alcohol
Nutritional deficiencies
Exposure to carcinogens



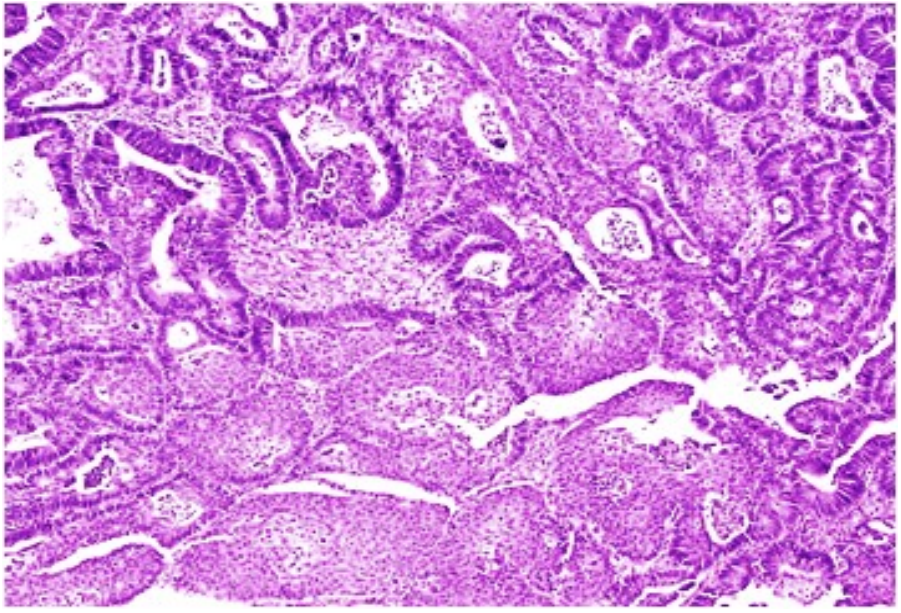
Solid black line adenocarcinoma; dashed line squamous cell carcinoma; dotted line not otherwise specified (SEER Data)

Carcinoma of the esophagus

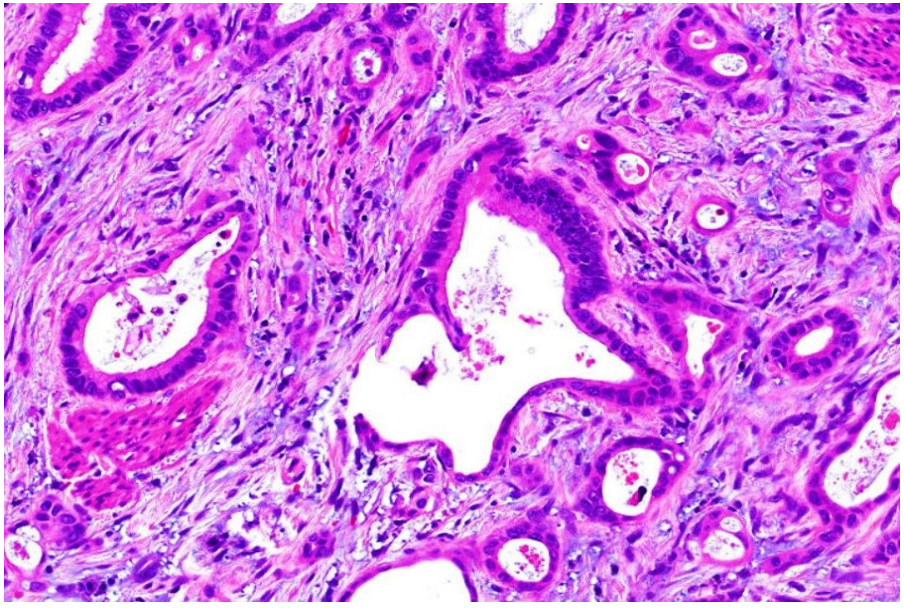
Type	Squamous cell carcinoma	Adenocarcinoma
Macroscopic		
Microscopic		



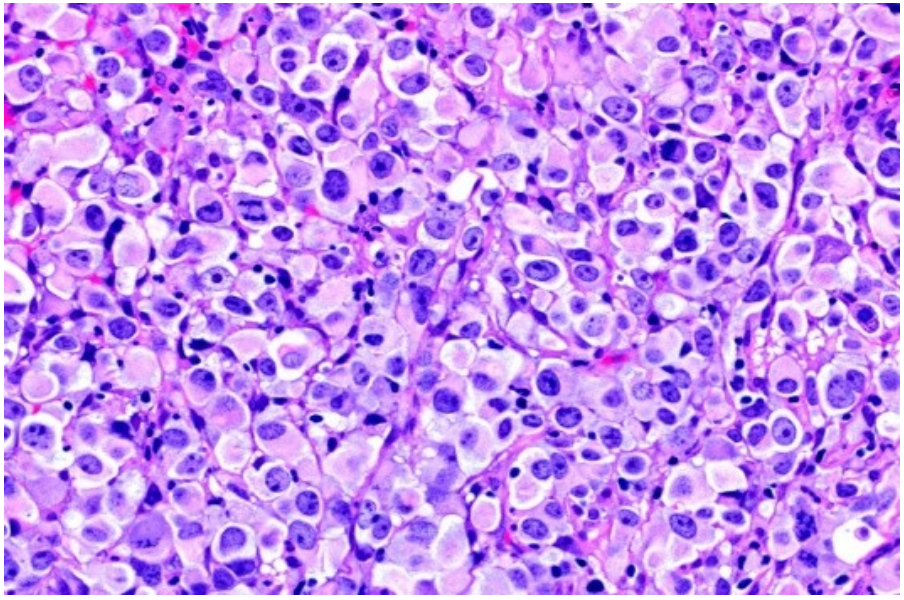
Squamous cell carcinoma



Adenosquamous carcinoma

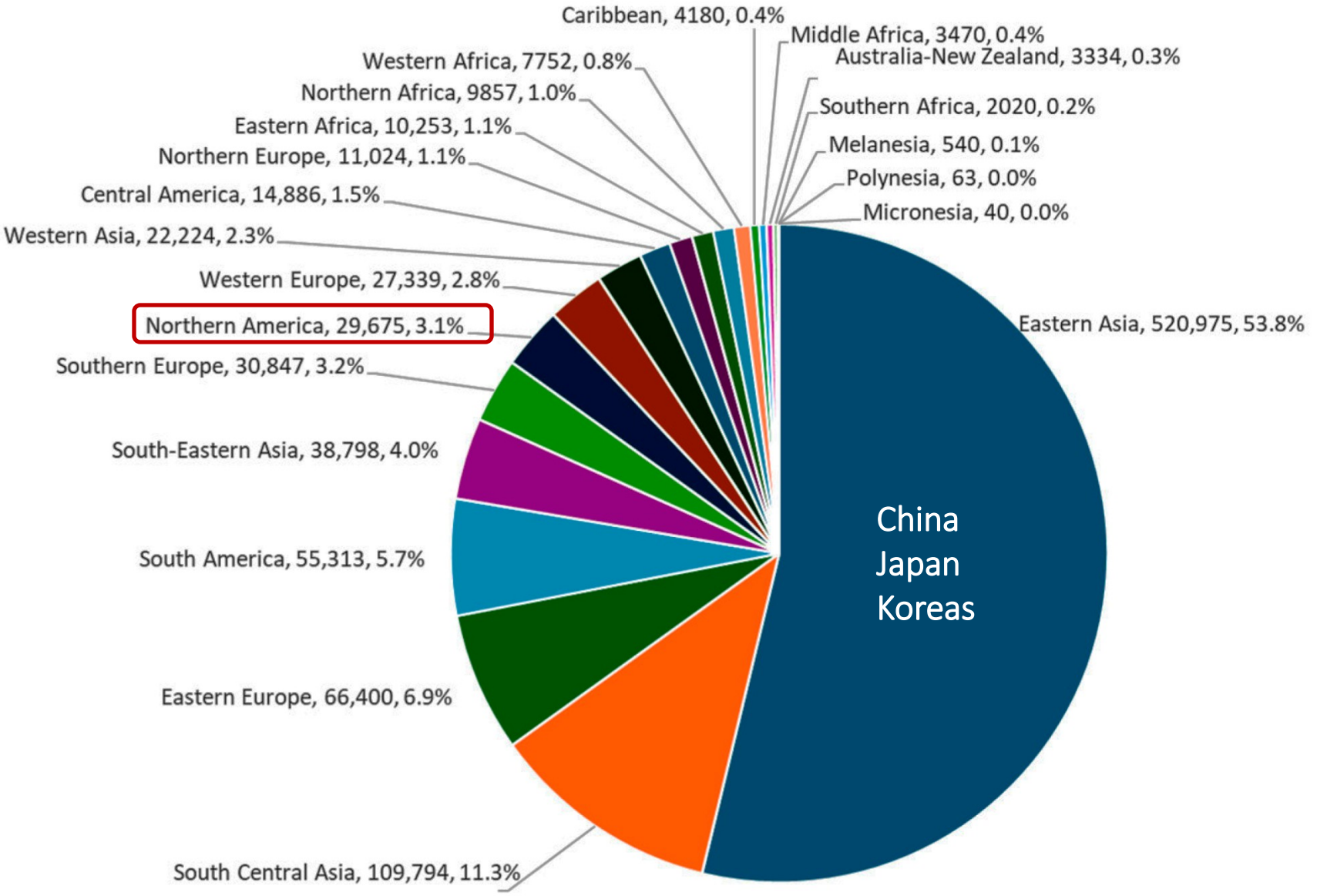


Adenocarcinoma



Undifferentiated carcinoma

Gastric Cancer epidemiology



Distribution of gastric cancer by UN region by absolute numbers in both sexes in 2022

Gastric cancer (2020)

1.2 million new cases (6% of all cancer cases)
1 million deaths (8% of all cancer deaths)
Ranks as **4th cause of cancer deaths**

75% of all new cases and all deaths reported in Asia.

East Asia (22.4 per 100000 people), Central and Eastern Europe (11.3 per 100000 people), South America, Polynesia and Western Asia (equally 8 per 100000 people)

Lowest rate (3.3 per 100000 people) reported in Southern Africa

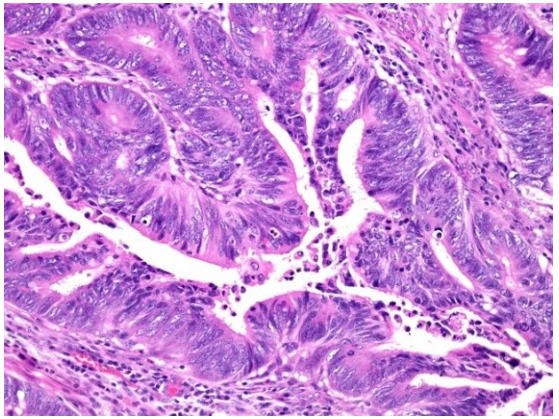
Five-year survival rate of around 20%.

Risk factors include *H pylori* infection, dietary factors, tobacco, obesity, and radiation

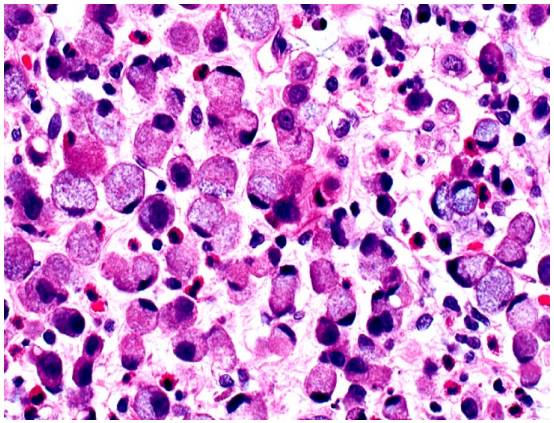
Gastric cancer	
Epidemiology	**Globally**, 5th most common malignancy and 4th leading cause of cancer
Incidence	**High risk areas** include **East Asia, Eastern, Central and Sothern Europe and South America** **Low incidence areas** included South Asia, North America, NZ, Australia, North and East Africa
Etiology	**H pylori** is most important risk factor in high-risk regions, 80% occurring in distal stomach **GERD** increase the risk of cancer, mostly occuring in upper stomach **Genetic factors** such as CDH1 mutation **Life style factors** (diet, smoking, alcohol, obesity , etc)
Trend	**Decline** in incidence and mortality during the past five decades (H pylori eradication, improved hygiene standards, etc)

Lauren classification of gastric cancer (1965)

Intestinal-type	50%
Diffuse-type	30%
Intermediate-type	15%
Mixed-type	5%

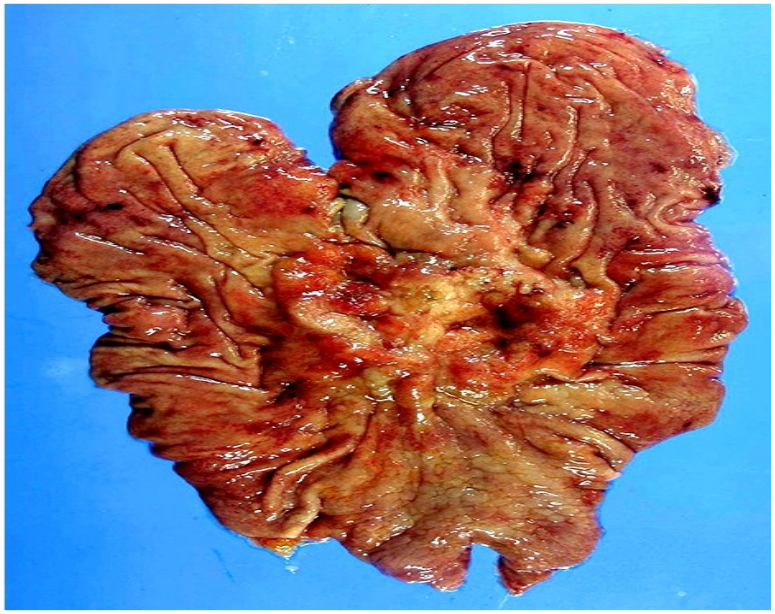


Intestinal-type

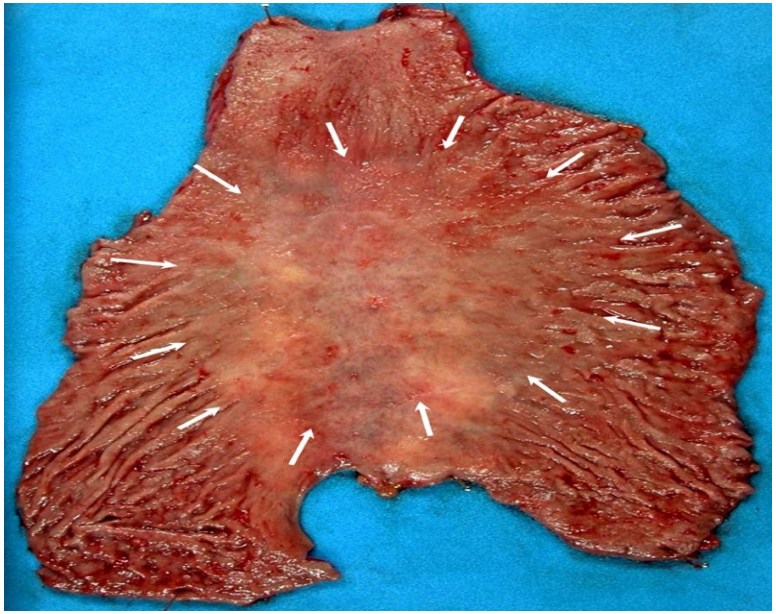


Diffuse-type

Lauren classification of gastric cancer (1965)	
Intestinal-type adenocarcinoma	**Diffuse-type adenocarcinoma**
Distal location	Proximal stomach
Nodular growth pattern	Diffuse flat growth pattern
Older people	Younger people
M:F ratio of 2:1	M:F ration of 1:1
Environmental factors	**Genetic factors**
Better prognosis	Worse prognosis



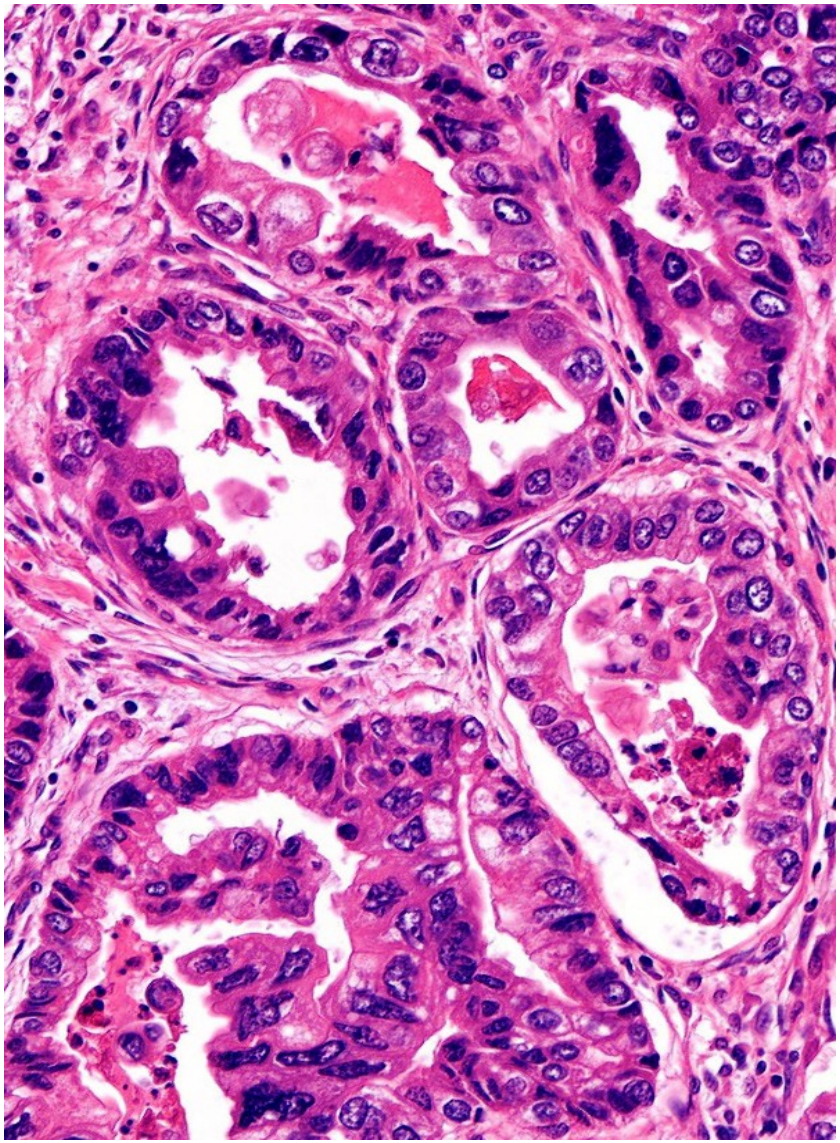
Intestinal type gastric adenocarcinoma



Diffuse type gastric adenocarcinoma

Intestinal-type gastric cancer

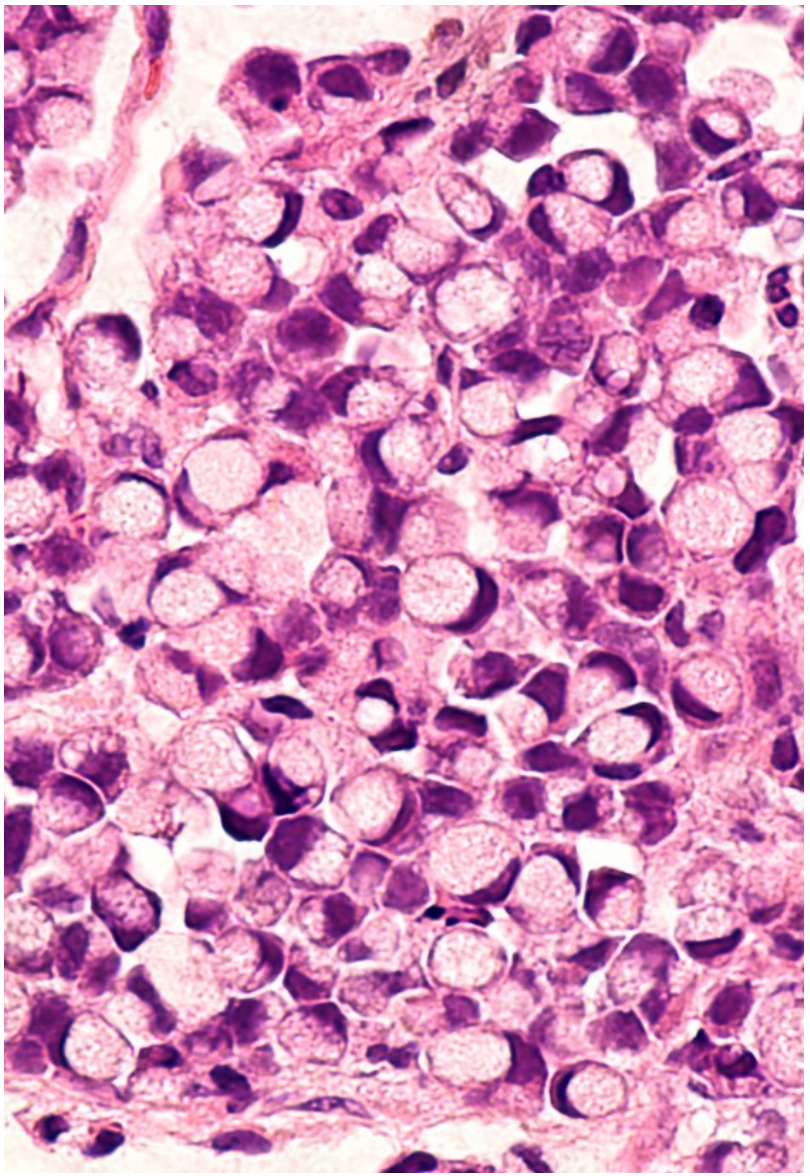
Nodular or ulcerative



Gland forming columnar cell

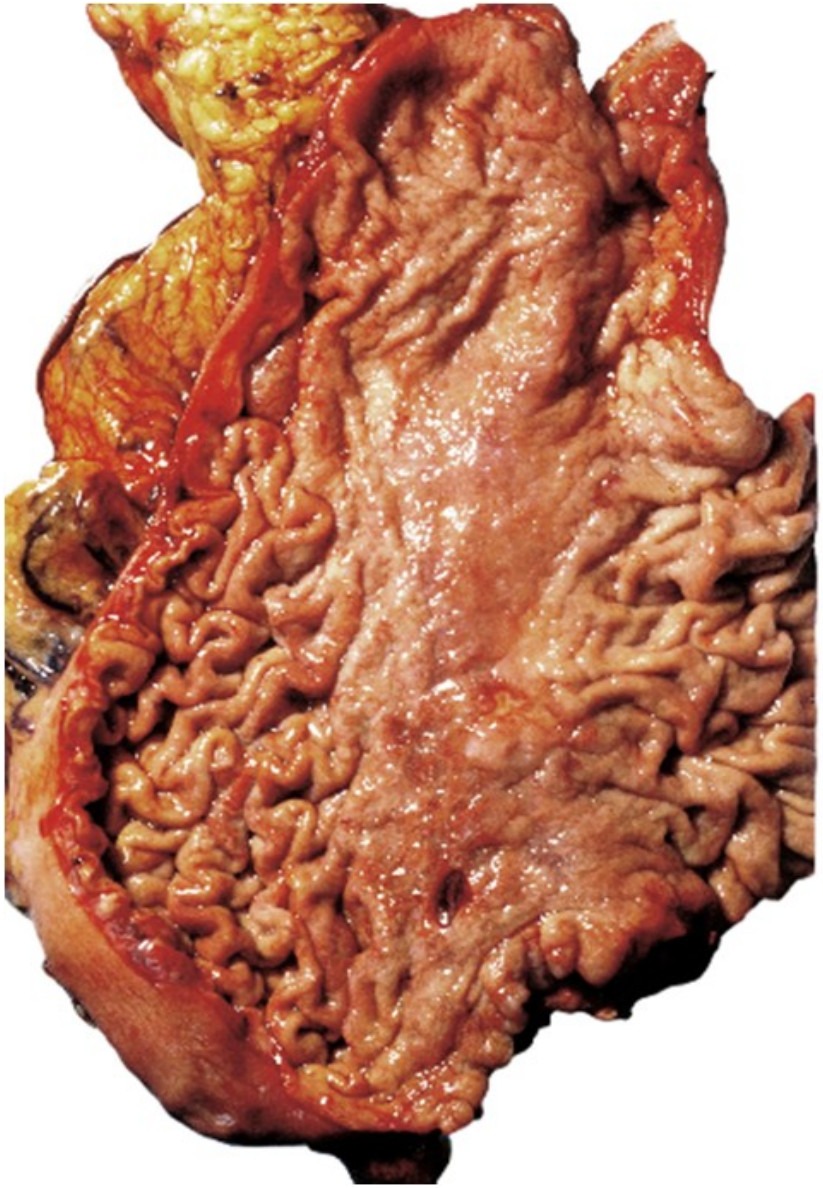
Diffuse gastric cancer

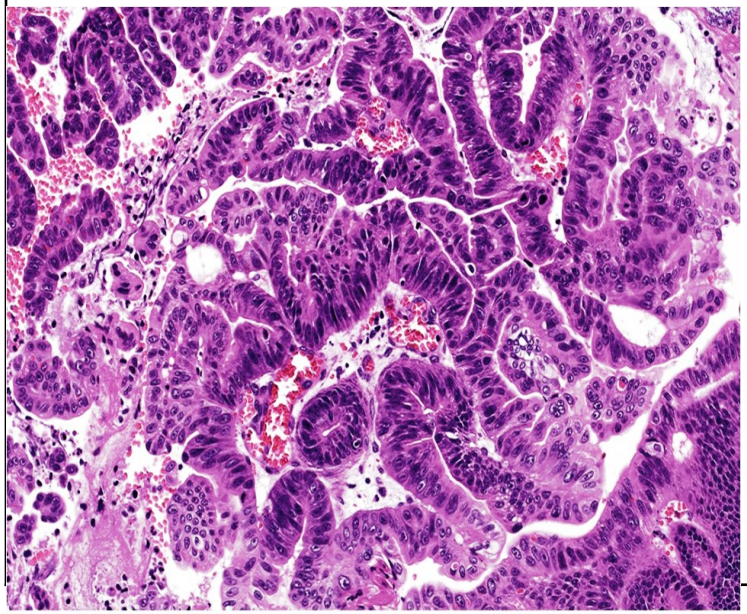
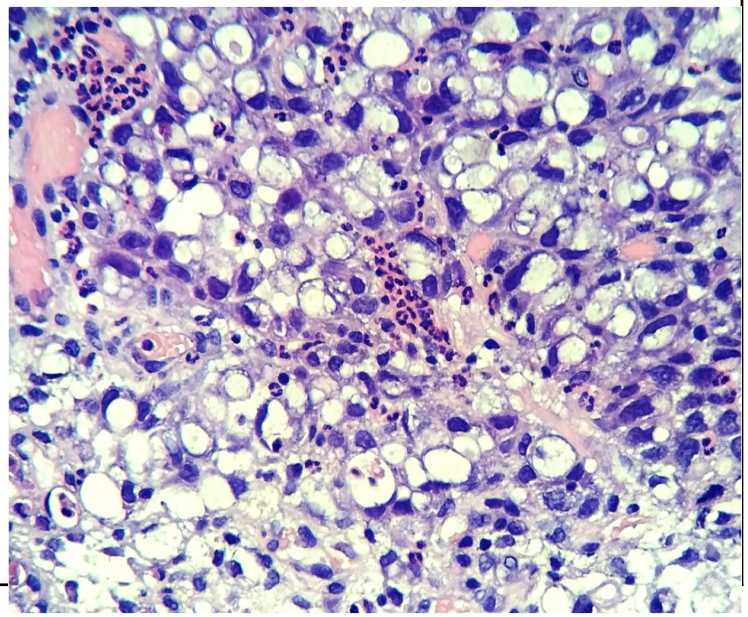
Flat and diffuse +/- ulceration



Dissociated signet ring cells

Diffuse gastric cancer



Gastric carcinoma classification	
Intestinal type adenocarcinoma	Diffuse adenocarcinoma
Glandular architecture Columnar cells Mucin +/- Background of H pylori gastritis Intestinal metaplasia Dysplasia	Single or small groups of cells Cellular discohesion Signet-ring appearance Cytoplasmic mucin droplets No H pylori background E-cadherin gene mutation
	

Pathogenesis of intestinal-type gastric adenocarcinoma

H pylori infection

⇩

Chronic gastritis with atrophy and intestinal metaplasia

⇩

LG dysplasia

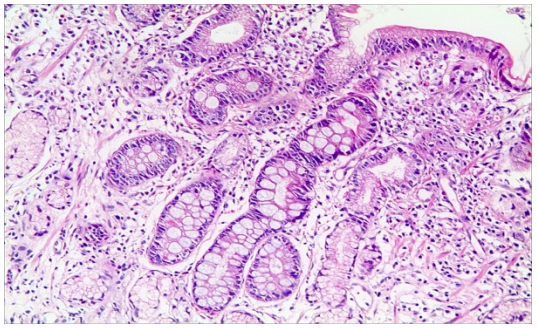
⇩

HG dysplasia

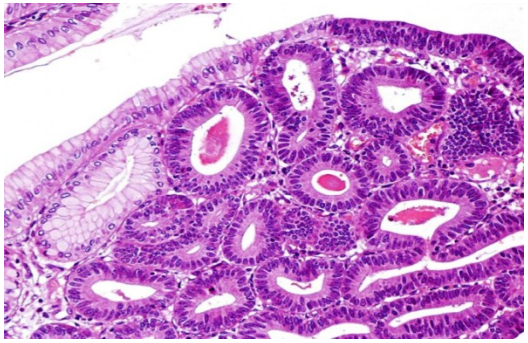
⇩

Invasive adenocarcinoma

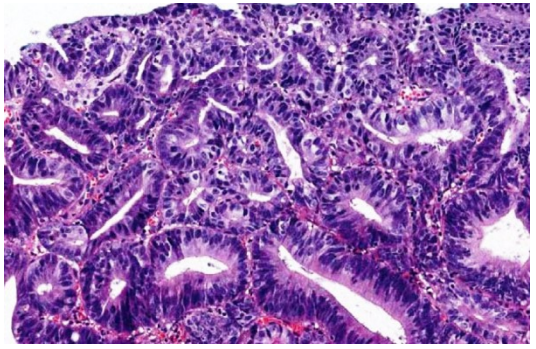
Chronic atrophic gastritis with intestinal metaplasia



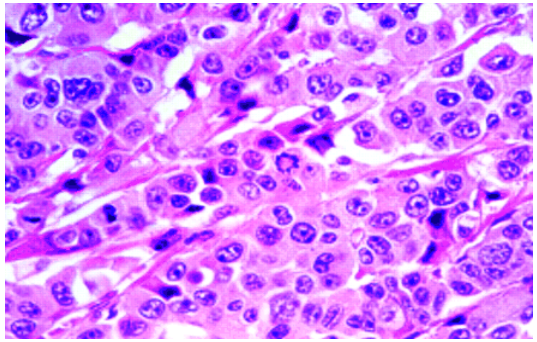
Low grade dysplasia



High grade dysplasia (in situ carcinoma)

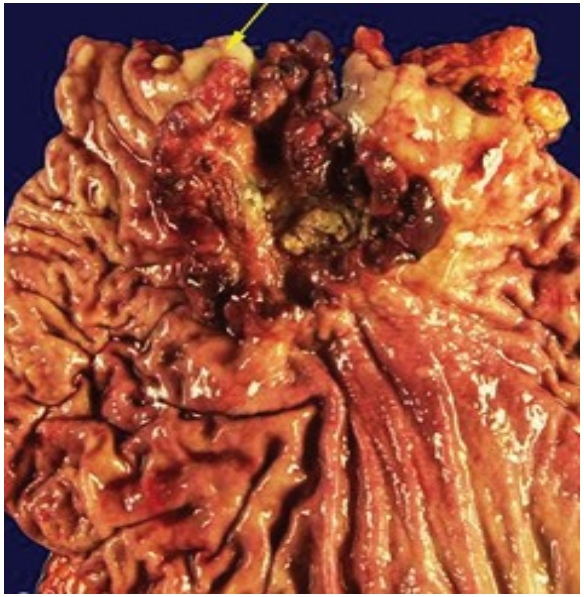


Adenocarcinoma



Gastric cardia cancer types	
GERD-associated pathway	Atrophic gastritis pathway
Resembles esophageal adenocarcinoma (EAC) Chronic inflammation due to bile acid containing duodenal reflux Higher acid production H. pylori-negative	Resembles non-cardia gastric cancer (intestinal type) H. pylori induced chronic inflammation with atrophy and intestinal metaplasia Low acid production Cardia is frequently infected with H. pylori and H pylori carditis develops when H. pylori shifts from distal to proximal stomach
Although the complete explanation the increase in cardia cancer and EAC cases remains undetermined, rising GERD rates may partially account for the rise	

Pathogenesis of gastric cancer	
Intestinal type	
Cardia 10%-20%%	Non-cardia >80%
Carditis (GERD) or H pylori infection Chronic injury Intestinal metaplasia Dysplasia Carcinoma	Chronic gastritis (H pylori) Atrophic gastritis Intestinal metaplasia Dysplasia Carcinoma



Intestinal-type adenocarcinoma vs diffuse-type adenocarcinoma		
	Intestinal-type	Diffuse-type
Age	Older age	Young age
Sex	M>F	M = F
Risk factors	Environmental factors (H pylori, others)	Genetic factors (E-cadherin or CDH1 gene mutation)
Histological precursors	Dysplasia or adenoma	?Signet ring in situ carcinoma
Surrounding mucosa	Atrophic gastritis with intestinal metaplasia	Normal mucosa No intestinal metaplasia
Common location	Distal (antrum)	Corpus
Gross features	Exophytic, ulcerative	Flat (linitis plastica)
Microscopic features	Well developed glands	Discohesive cells, signet ring
Routes of dissemination	Lymphovascular spread	Direct and LV spread

Lauren classification of gastric cancer (1965)

Intestinal-type

Diffuse-type

Intermediate-type

Mixed-type

WHO Classification 2019

Adenocarcinoma
- Tubular adenocarcinoma
- Parietal cell carcinoma
- Adenocarcinoma with mixed subtypes
- Papillary adenocarcinoma
- Micropapillary carcinoma
- Mucoepidermoid carcinoma
- Mucinous adenocarcinoma
- Signet ring cell carcinoma
- Poorly cohesive carcinoma
- Medullary carcinoma with lymphoid stroma
- Hepatoid adenocarcinoma
- Paneth cell carcinoma

Squamous cell carcinoma

Adenosquamous carcinoma

Carcinoma, undifferentiated

The Cancer Genome Atlas (TCGA) Project Molecular Classification 2013		
Chromosomal Instability (CIN)	50%	GEJ/cardia Intestinal –type histology P53, SMAD4, APC mutation KRAS mutation Intermediate prognosis
Genomically Stable (GS)	20%	Proximal stomach Diffuse –type histology CDH1/RHOA mutations Loss of cell adhesion Worst prognosis
Microsatellite Instability (MSI)	20%	Older female Distal stomach Intestinal histology CIMP MLH1 silencing Best prognosis
Epstein-Barr Virus (EBV)	10%	EBV-CIMP positive PDL1 overexpression PIK3CA and ARID1A mutations CDKN2A silencing Immune cell signaling Intermediate prognosis

Histological

Lauren Clssification

Intestinal Type

Diffuse Type

Indeterminate Type

WHO Classification

Papillary Adenocarcinoma
Tubular Adenocarcinoma
Mucinous Adenocarcinoma

Poorly cohesive types
Signet ring Carcinoma

Mixed carcinoma
Adenosquamous Carcinoma
Squamous cell carcinoma
Hepatoid adenocarcinoma
Carcinoma with lymphoid stroma
Choriocarcinoma
Carcinosarcoma
Parietal cell carcinoma
Malignant rhabdoid tumor
Mucoepidermoid carcinoma
Paneth cell carcinoma
Undifferentiated carcinoma
Mixed adeno-neuroendocrine
Endodermal sinus tumor
Embryonal carcinoma
Pure gastric yolk sac tumor
Oncocytic adenocarcinoma

Molecular

TCGA

EBV
DNA hypermethylation
PIK3CA mut
ARIAD1A mut
PD-L1/PDL2 amp
CDKN2A silencing

MSI
Hypermutation
MLH1 silencing
PIK3CA mut
Older Patients
Intestinal Subtype

Genomic Stable
CDH1 and ROHA mut
CLDN18-ARHGAP fusion
Younger patients
Diffuse subtype

Chromosomal Instable
RTK-RAS activation (ERB2, EGFR MET, VEGFA, KRAS or NRAS)
Cell genes amp(CCNE1, CCND1 and CDK6)
TP53 mut
Intestinal Subtype

ACRG

MSS/TP53+
Intact TP53- activity signature (CDKN1A, MDM2)
EBV infection
Intestinal Subtype
Intermediate prognosis

MSI
MLH1 loss of expression
Elevated DNA methylation signature
Hypermutation
Best Prognosis / Intestinal sub

MSS/EMT
CDH1 loss expression
Less frequent mutation events
Worst Prognosis
Diffuse Subtype

MSS/TP53-
Loss of TP53 acstivity signature (CDKN1A, MDM2)
TP53 mut
Genomic instability
Oncogene Amp
Intermediate prognosis

Why is it important to know whether a cancer is MSS or MSI?
Can influence treatment decisions and prognosis

Treatment Decisions:

MSI-H stomach cancers can be treated with **immune checkpoint inhibitors**

Prognosis:

MSI-H cancers have a **better prognosis** compared to MSS cancers

Histological Type:

MSI is more commonly found in the **intestinal type**

Early Stage Diagnosis:

MSI-H cancers are more **likely to be diagnosed at an earlier stage**

Immunosurveillance:

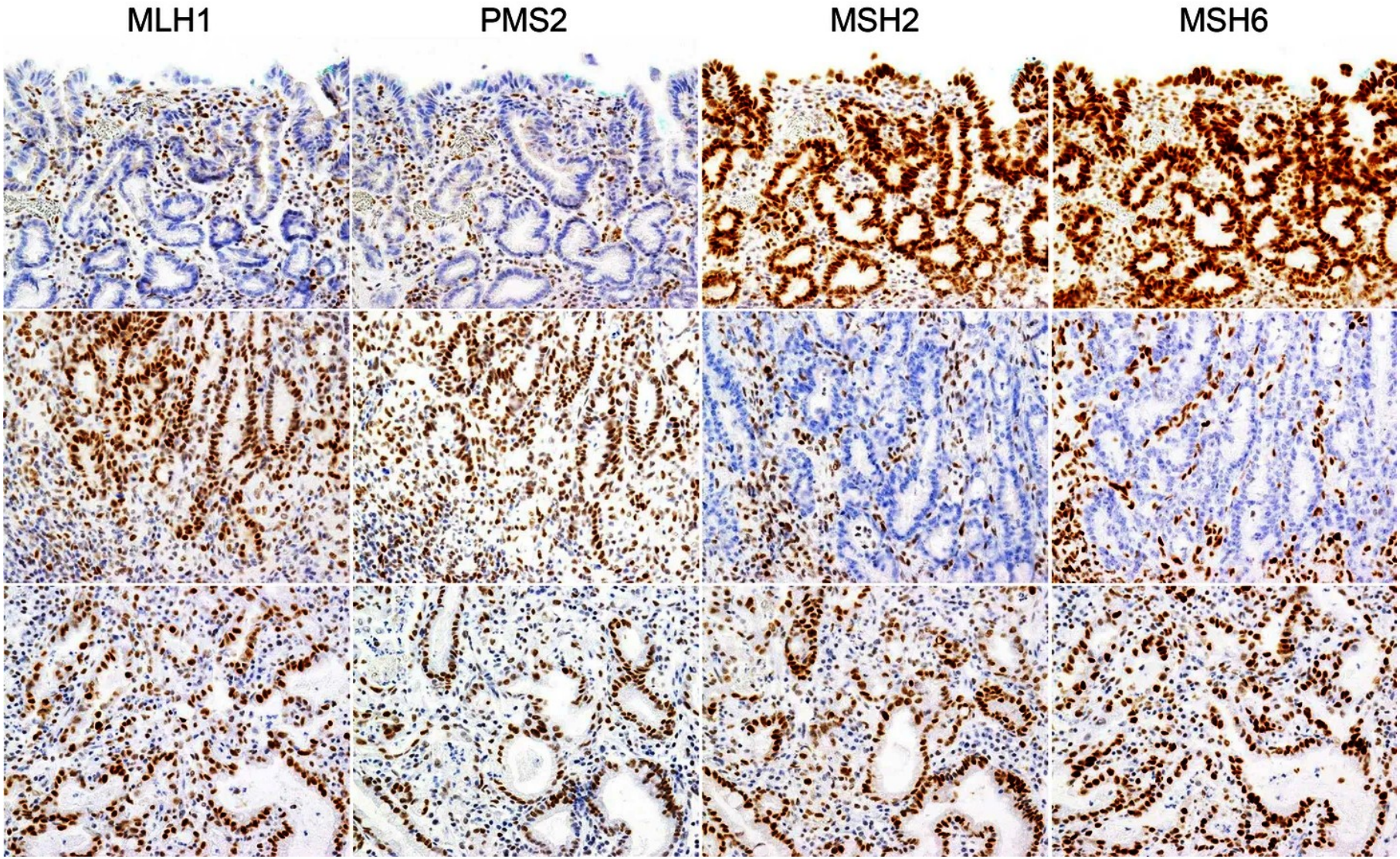
MSI-H cancers **trigger the immune system**, hence more likely to respond to immunotherapy.

Chemotherapy Response:

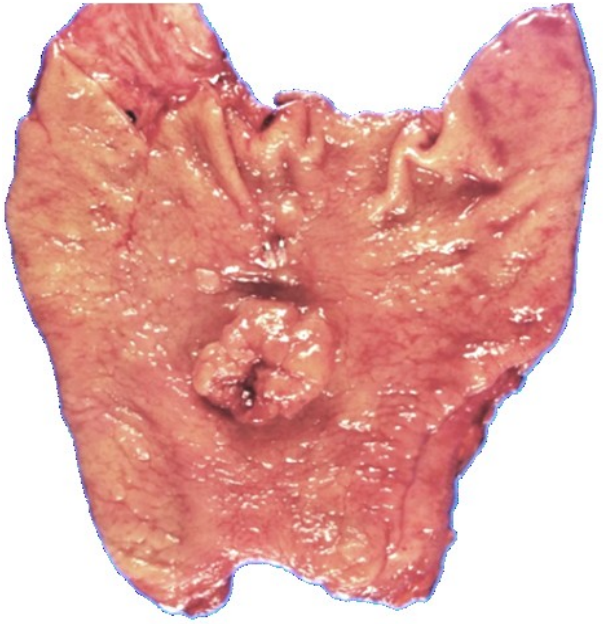
Studies suggest that MSI cancers may **not benefit from chemotherapy**.

Genetic Testing:

Guides genetic testing to identify those at **risk of inherited cancer syndromes**



MMR proteins by IHC. Upper panels show loss of MLH1 and PMS2 but retention of MSH2 and MSH6 (MLH1 and PMS2 deficient). Middle panels show loss of MSH2 and MSH6nbut retention of MLH1 and PMS2 (MSH2 and MSH6 deficient). Lower panels show MMR expressions of all 4 proteins (Proficient)

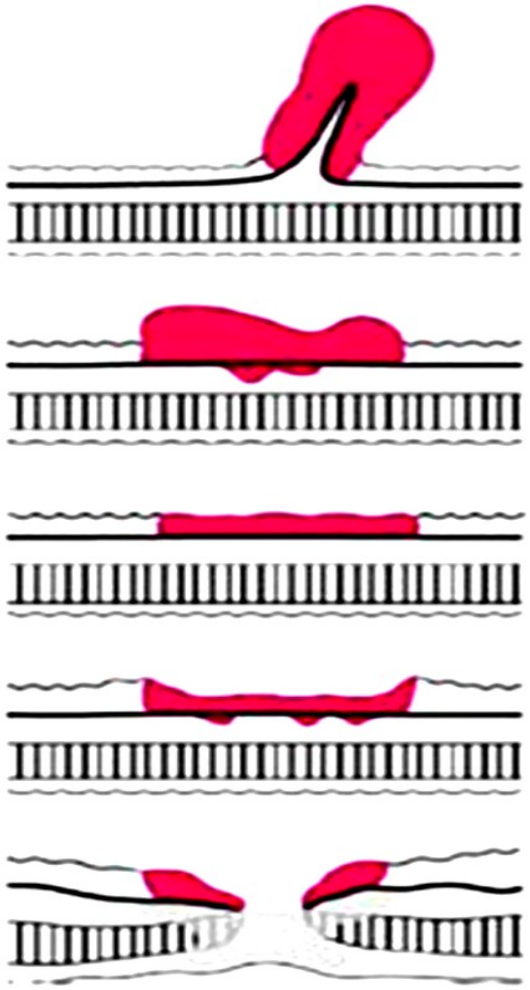


Intestinal-type gastric cancer

Diffuse-type gastric cancer

Early gastric cancer (EGC)

- Invasive adenocarcinomas confined to the **mucosa and submucosa** with no extension into the muscularis propria, regardless of nodal status or hepatic involvement (Japanese literature)
- **Protruded, elevated, flat, depressed, excavated or combined**
- **Mostly in distal stomach** with 10% being multicentric
- **Histology** is similar to late intestinal type gastric adenocarcinoma
- **Excellent results** (cure rate of about 90%)
- Amendable to **endoscopic treatment**



EGC represents over 50% of cases in **Japan and in South Korea**, whereas it accounts for approximately 20% of all newly diagnosed gastric cancers in Western countries.

Prognostic pathological factors

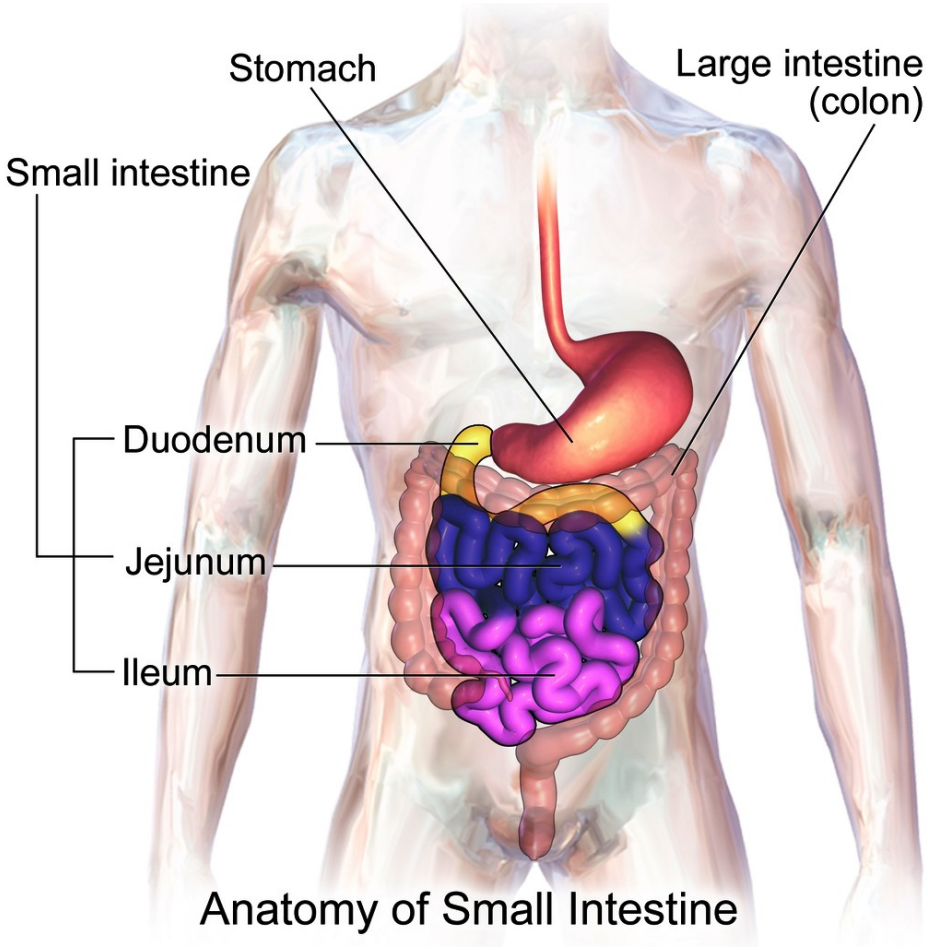
Overall prognosis of gastric cancer is **poor**

Tumour stage is the most powerful determinant of prognosis

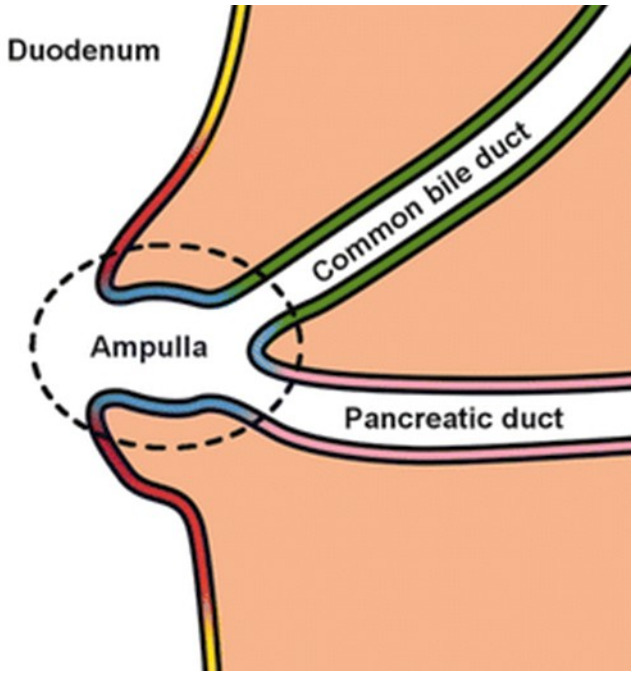
Histology is less important but survival is slightly higher in **intestinal-type than** in **diffuse-type**

Predictive markers (HER2, MSI and PDL1) may increase progression-free and overall survival

Carcinomas of the small intestine

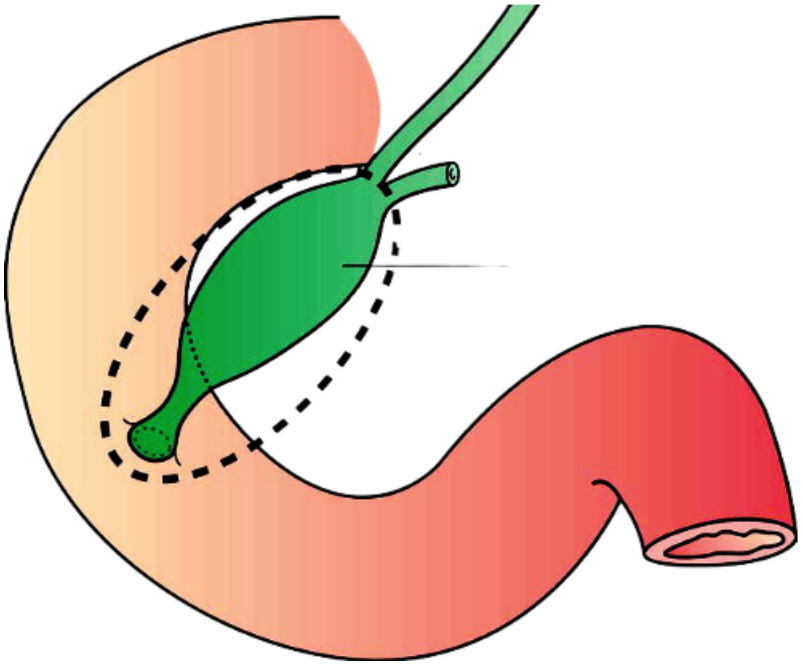


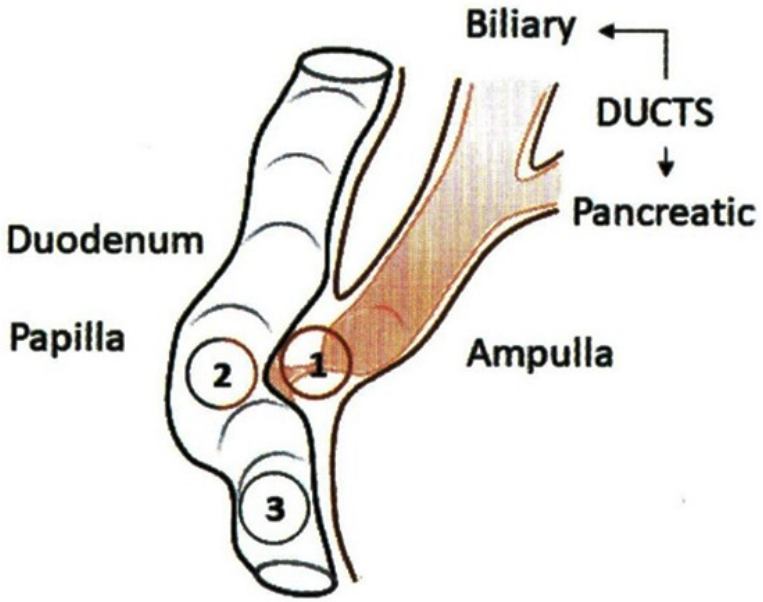
Small bowel carcinomas		
Relatively **uncommon** tumors		
Classified as **ampullary and non-ampullary** tumours		
Striking predilection for the **ampullary region**		
Prevalence of non-ampullary carcinomas decreases from the duodenum (60%) to Jejunum (30%) ileum (10%)		
Most are **sporadic** (no apparent cause) Some arise in the setting of **chronic inflammation** Others are seen in **hereditary cancer syndromes**		
Ampullary		Non-ampullary
Periampullary	Intra-ampullary	Duodenum, Jejunum, Ileum
Intestinal type histology	Pancreatobiliary type histology	Intestinal type Pyloric gland type



Ampulla of Vater

Complex area, about 1 cm long where the biliary, pancreatic and intestinal tracts converge





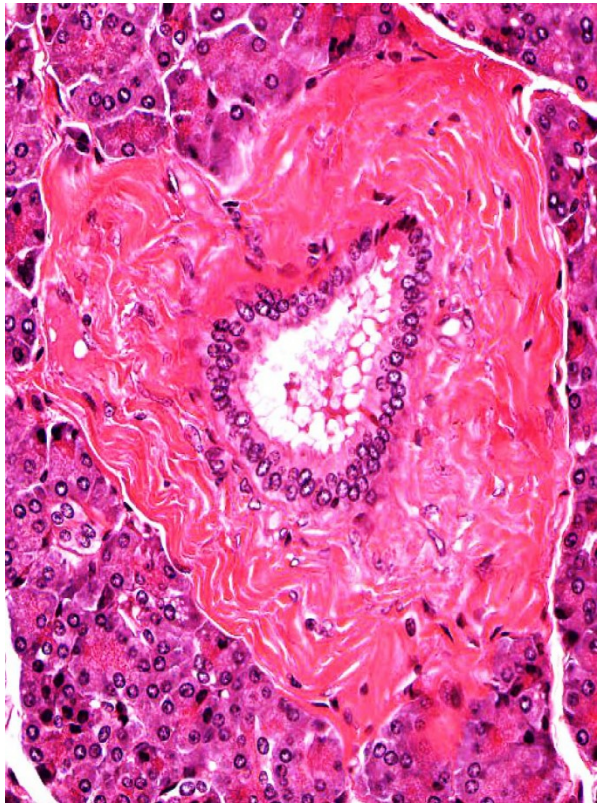
1 Ampullary duct

2 Periampullary (duodenal) area

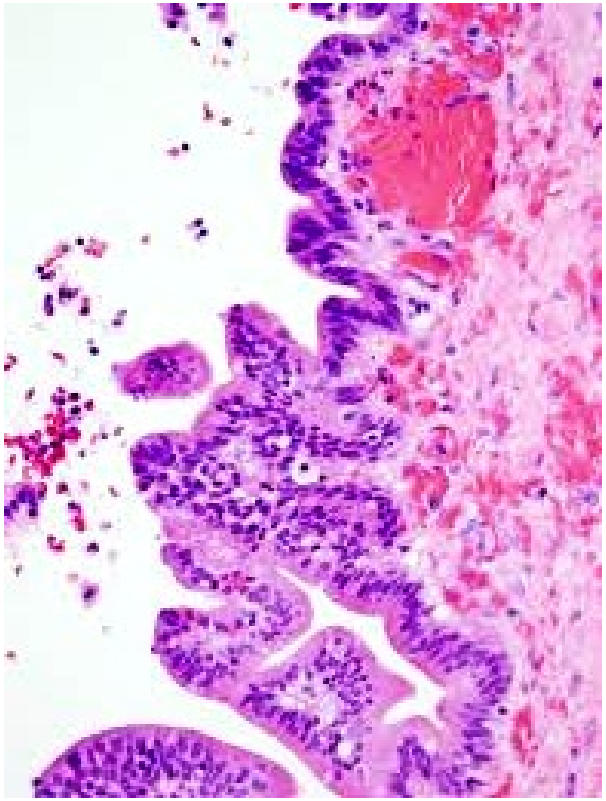
3 Extra-ampullary (duodenal) area

Types of epithelium in the ampullary region

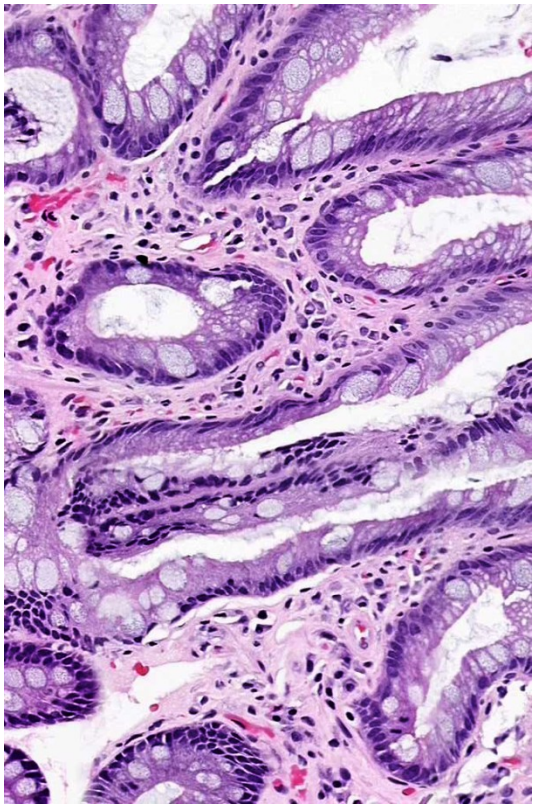
Pancreatic epithelium



Biliary epithelium

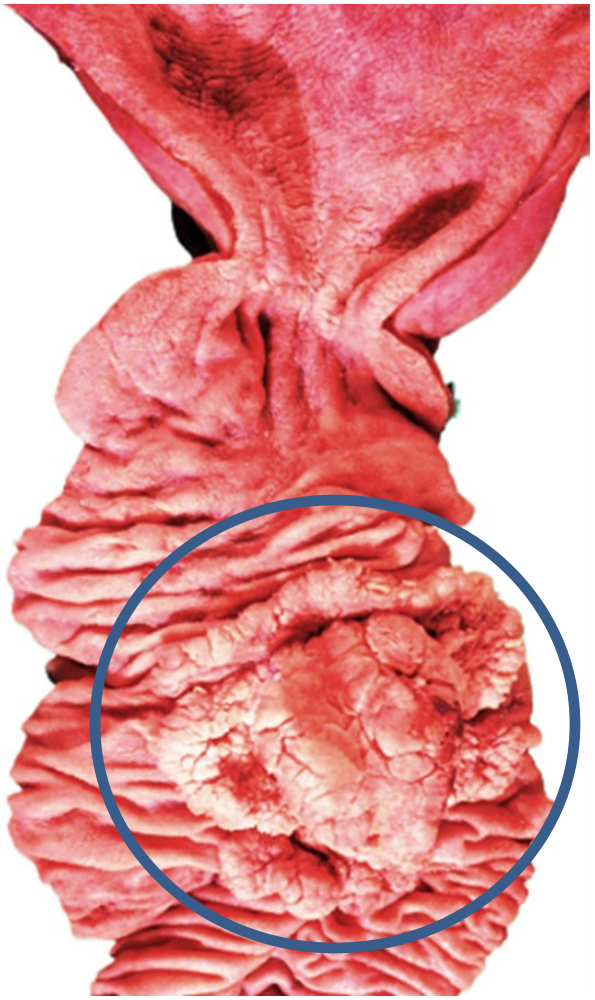


Intestinal epithelium

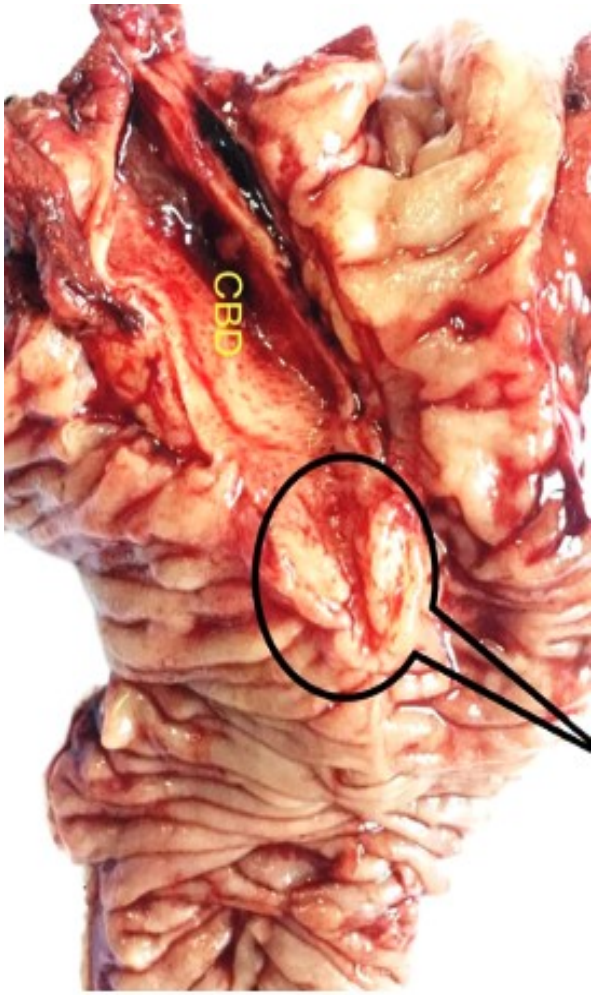


Small bowel carcinomas

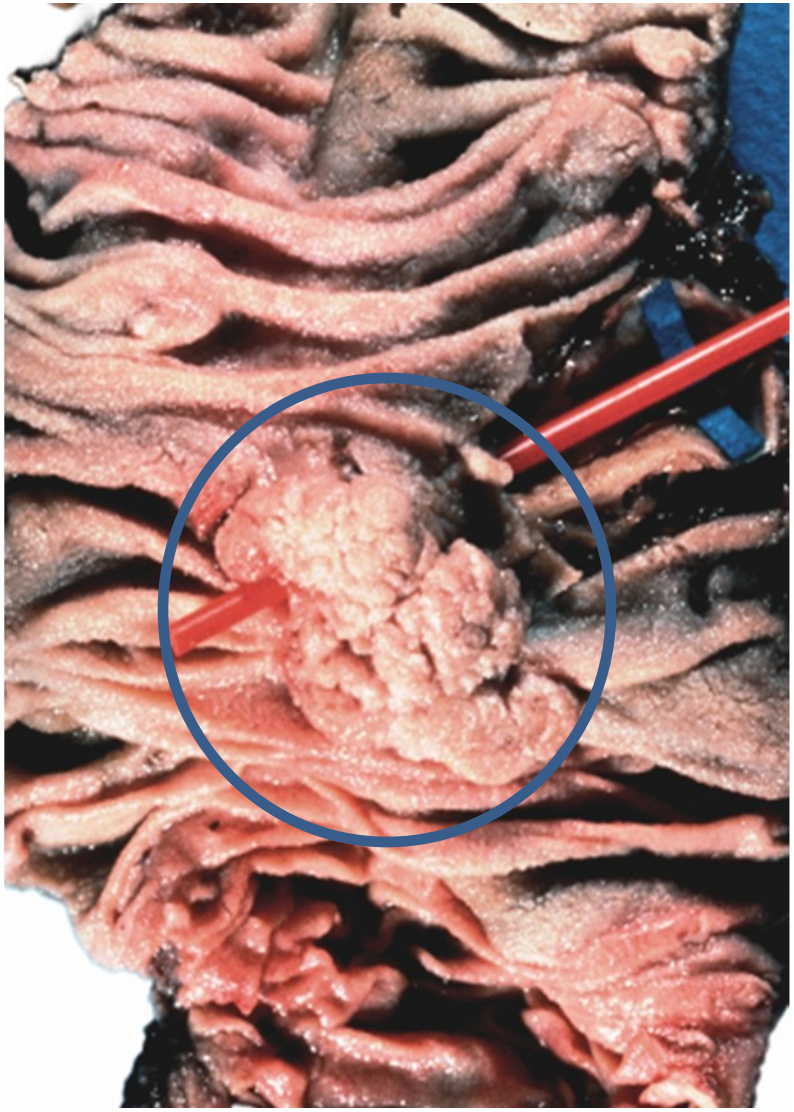
Non-ampullary carcinoma



Peri-ampullary carcinoma



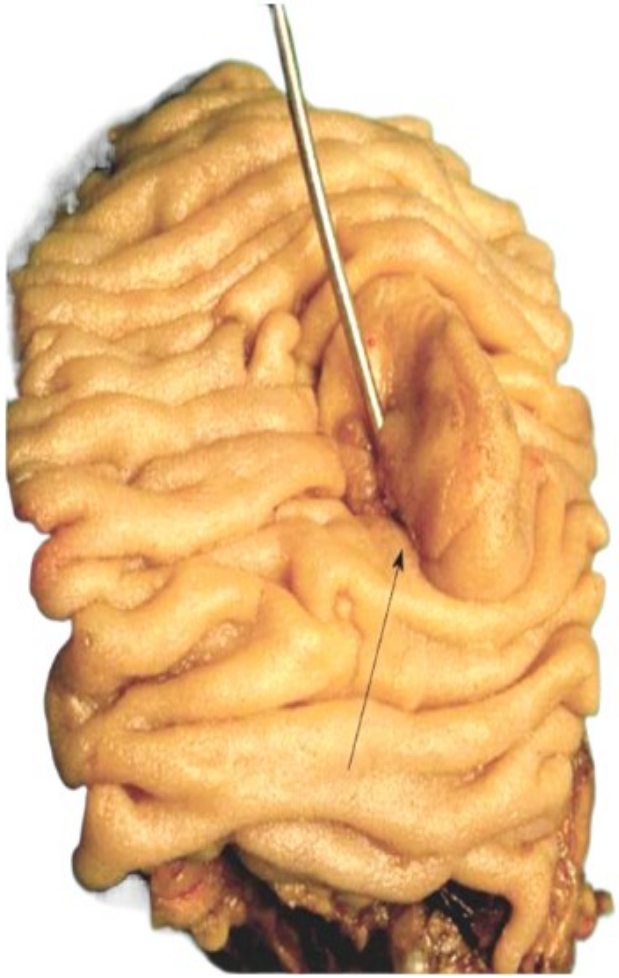
Intra-ampullary carcinoma

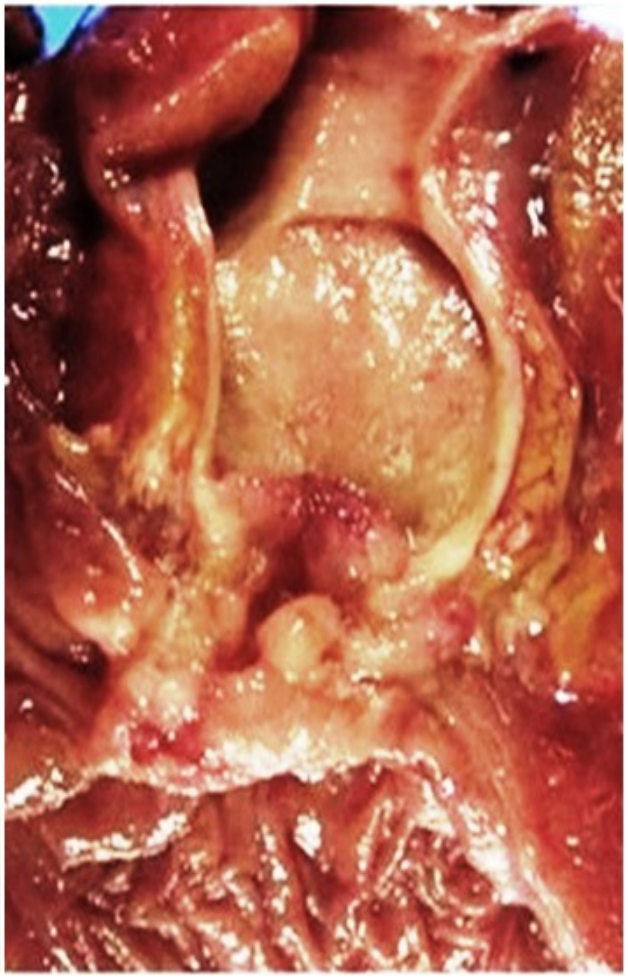


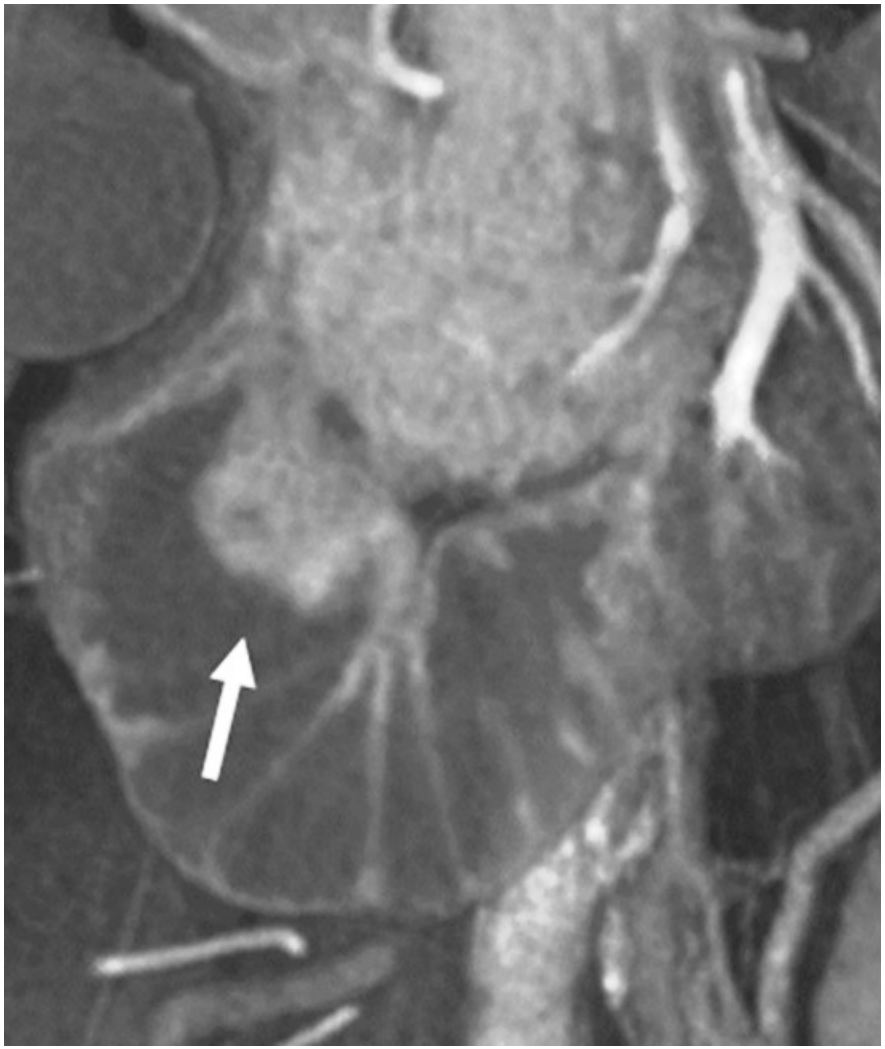
Periampullary carcinoma

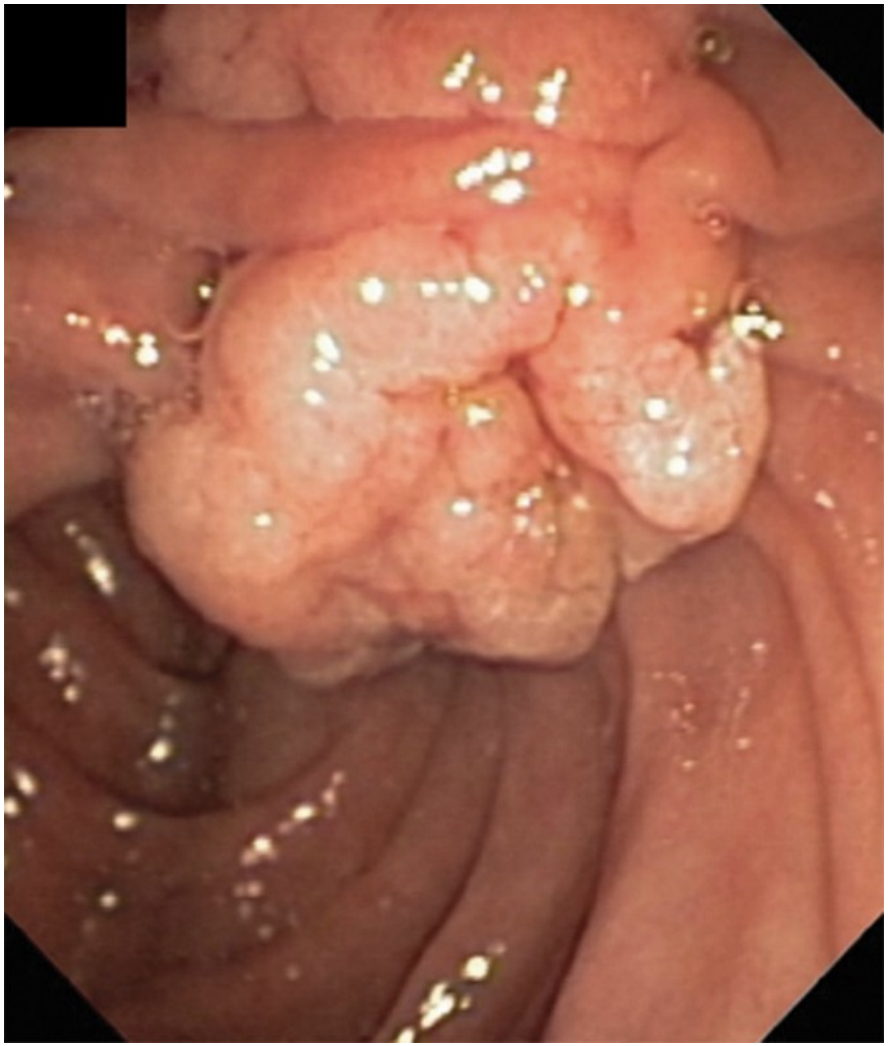
Peri-ampullary carcinoma

Intra-ampullary carcinoma

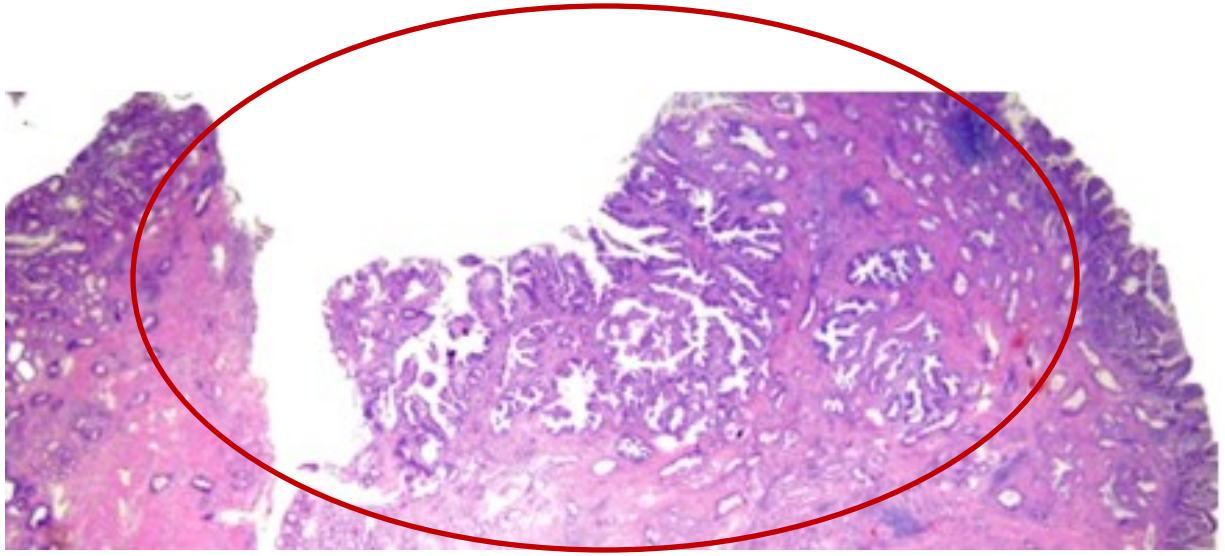






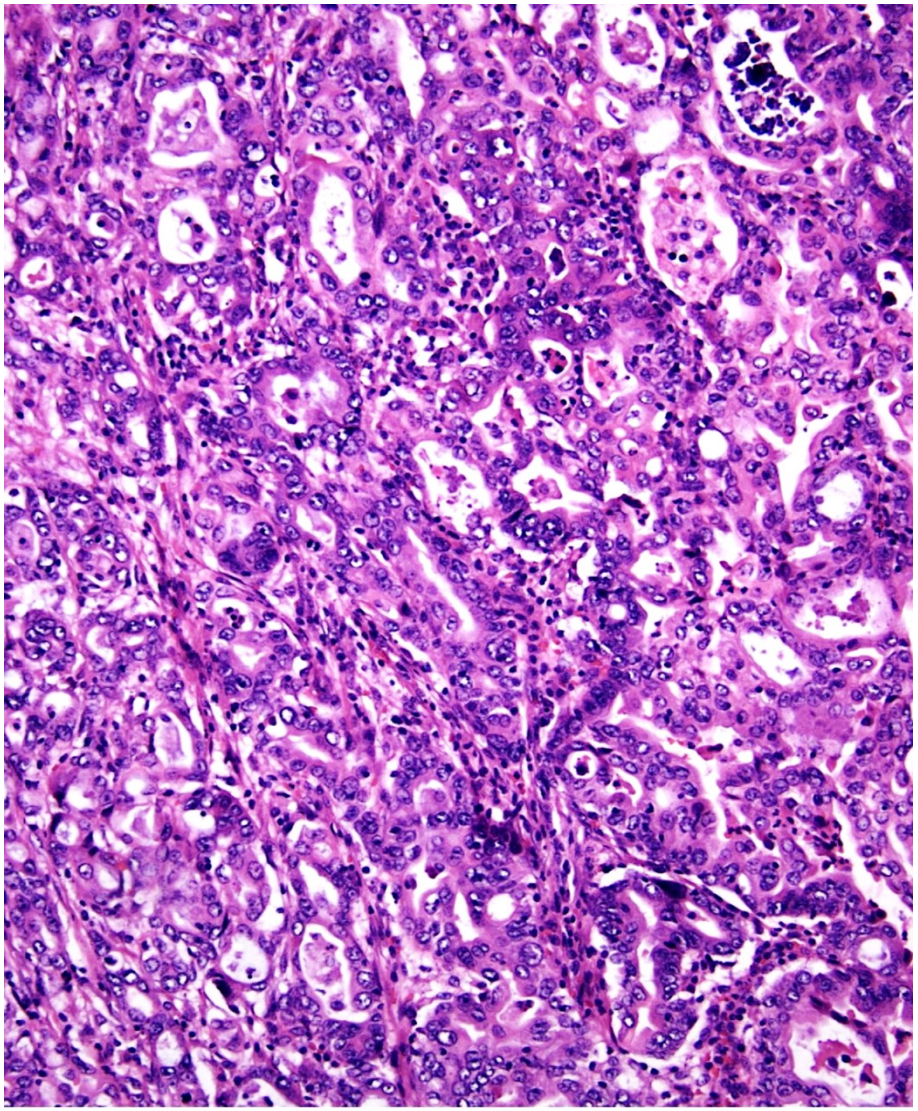


65-year-old man with **intestinal subtype ampullary adenocarcinoma** presenting with **jaundice**. Slightly hypodense, **nodular ampullary tumor** in a distended duodenum.

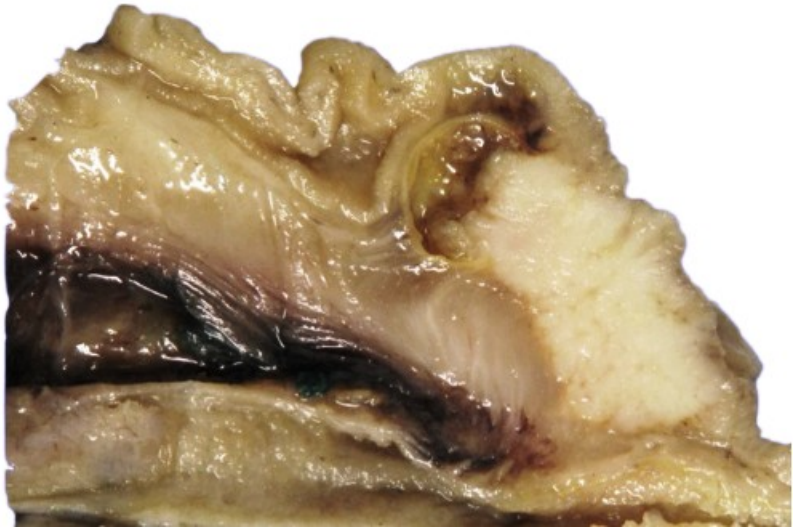


55-year-old man with jaundice and intra-ampullary adenocarcinoma of pancreatobiliary subtype with tubulopapillary growth pattern and low columnar cell type

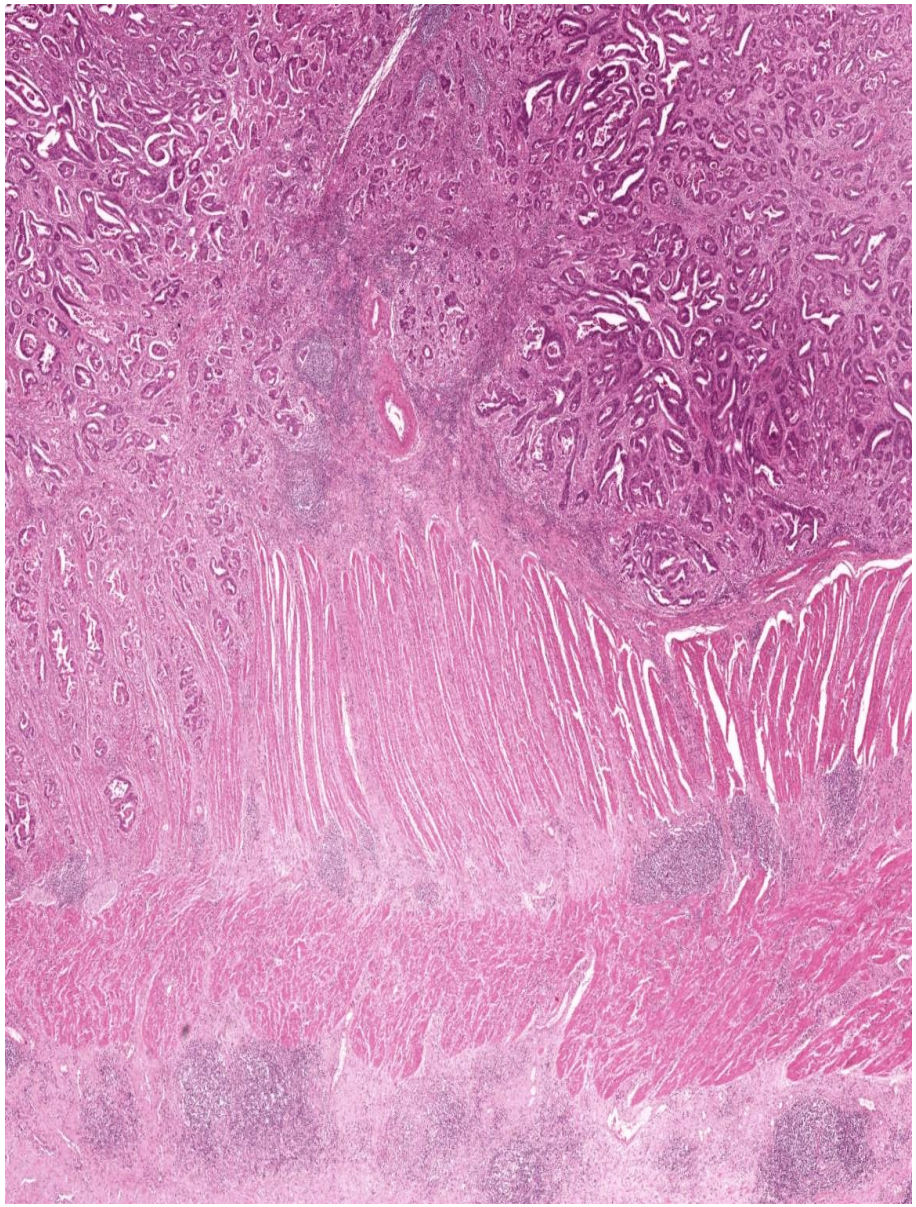
Intestinal (left) and pancreatobiliary (right) subtypes



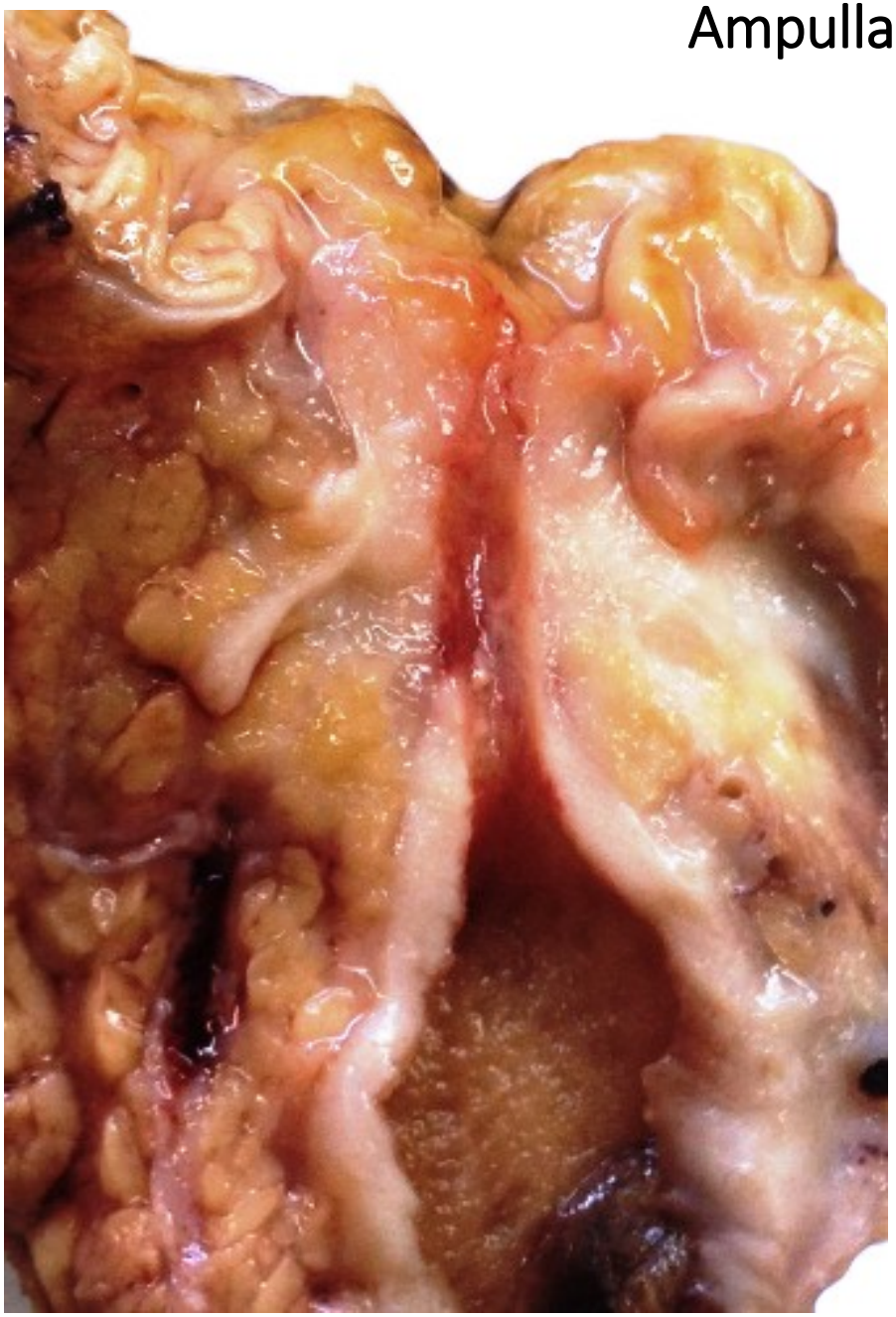
Non-ampullary carcinomas

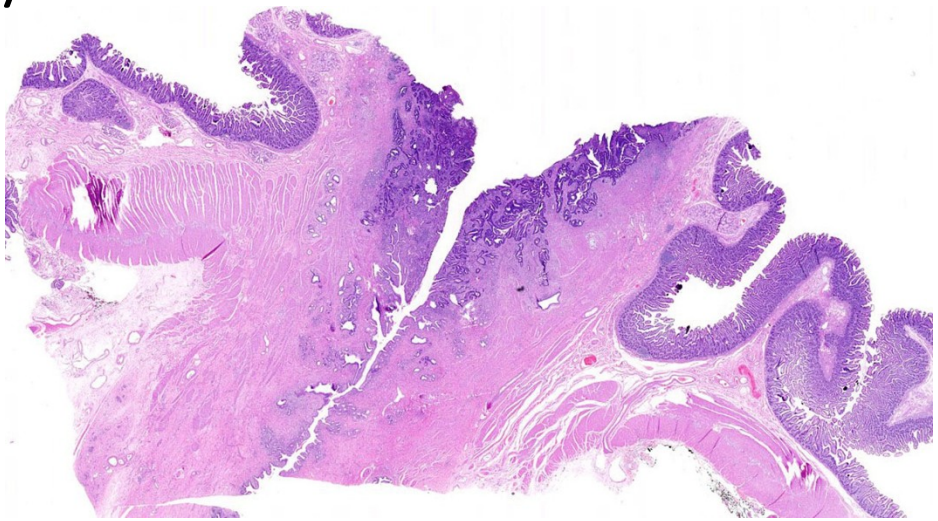


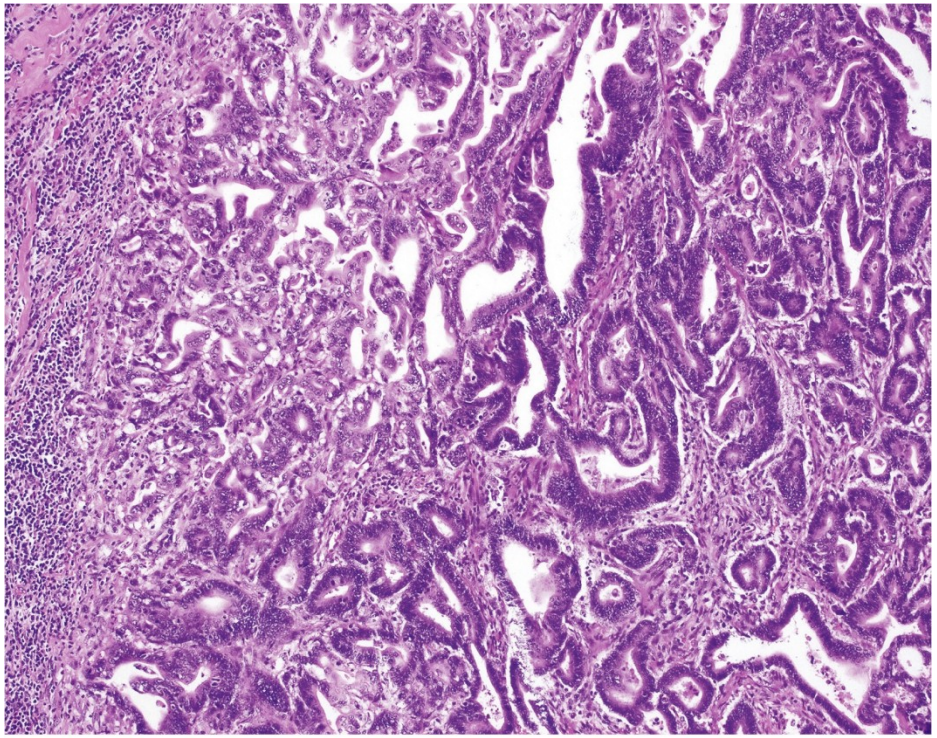
Non-ampullary carcinomas

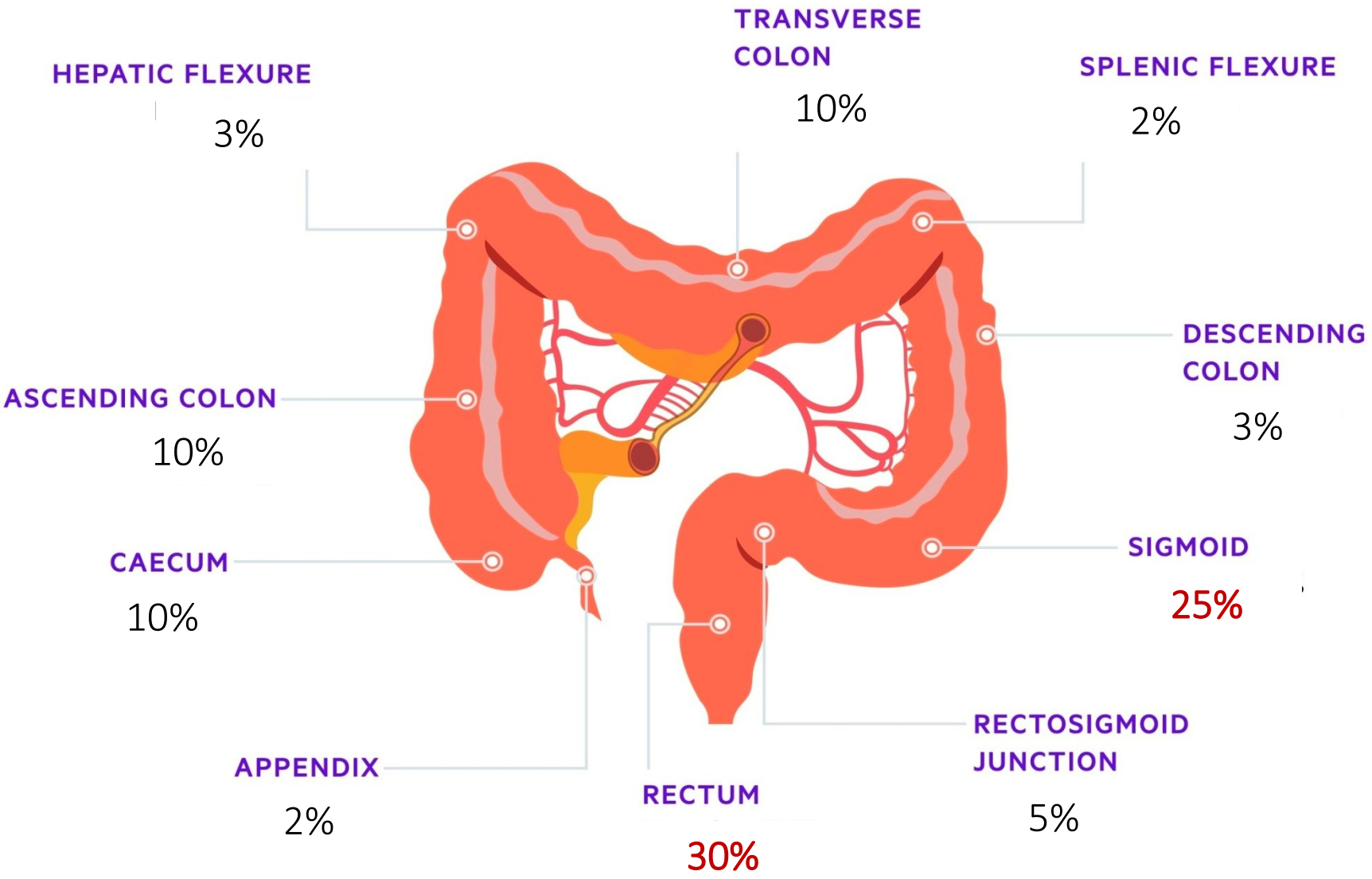


Ampullary carcinomas





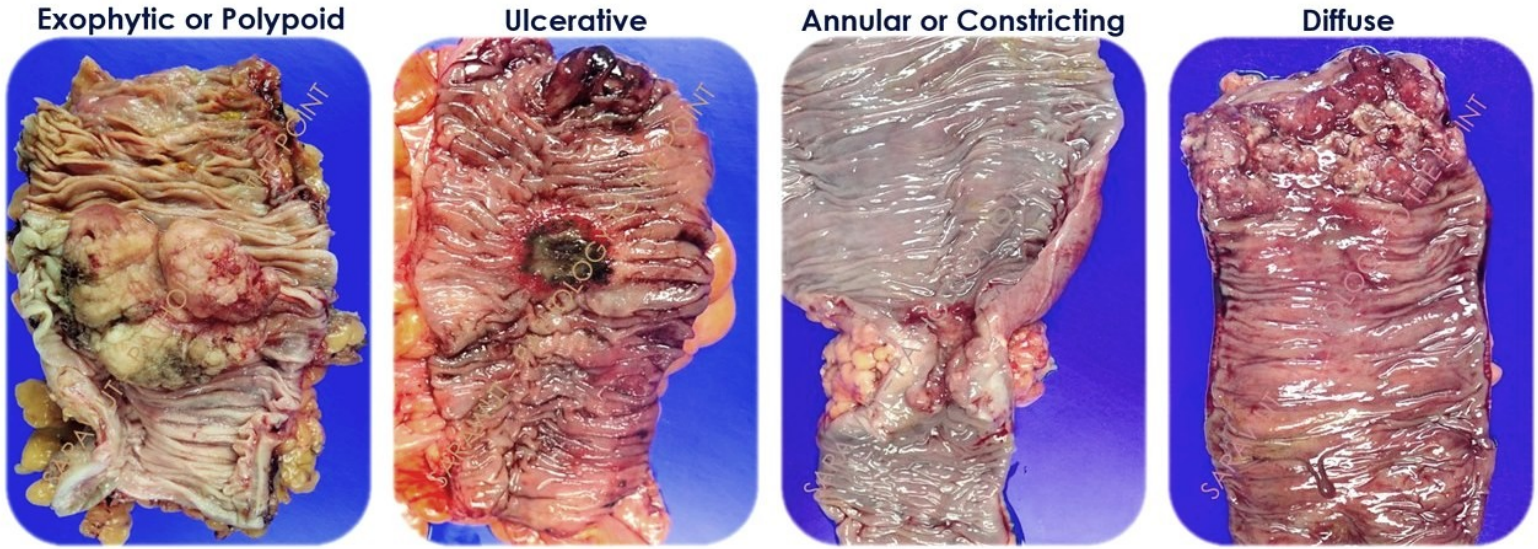




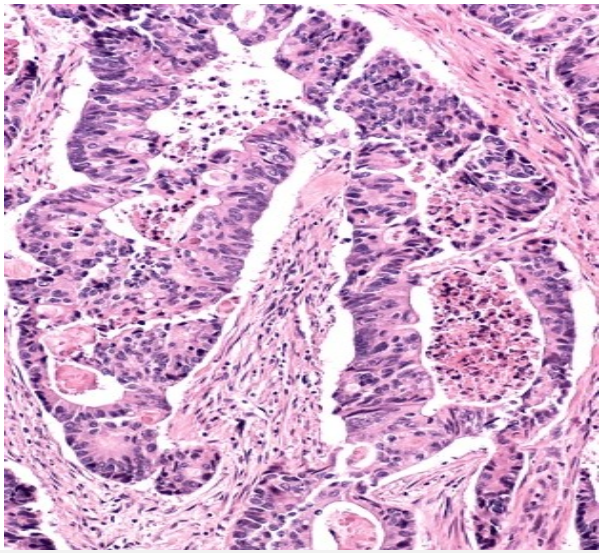
Colorectal Carcinomas

Clinical features of colorectal cancer

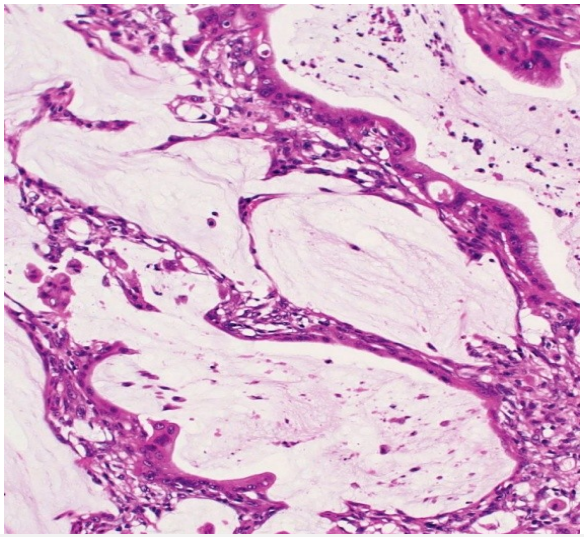
- Almost all are **adenocarcinomas**
- Most arise within **adenomas ; some arise from dysplasia (IBD)**
- Develop **slowly** and may go undetected for **long periods**
- **Right colon cancers** grow as **exophytic masses** and present with **fatigue and weakness** (iron deficiency anemia)
- **Left colon cancers** grow as **constricting lesions** and may produce occult bleeding, bowel habit change or obstruction


Exophytic or Polypoid
Ulcerative
Annular or Constricting
Diffuse
▪ Cecum & Ascending colon
▪ Rarely obstruction
▪ Quite large before clinical presentation
▪ Unexplained iron deficiency
▪ Irregular edges and a central, excavated ulcer
▪ Ulceroproliferative
▪ Melena / Hematochezia
▪ Distal or left colon
▪ Ulceroinfiltrative
▪ "Apple-core" or "Napkin-ring" lesion
▪ Bowel obstruction
▪ Uncommon type
▪ Diffuse thickening of the colon
▪ Analogous to linitis plastica of the stomach

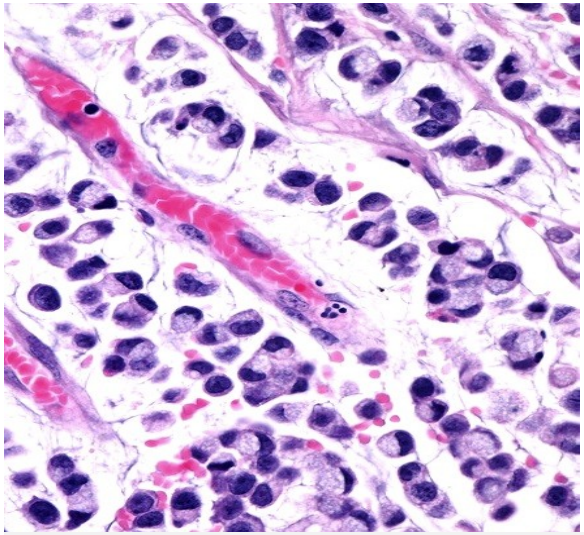
Histological types of colorectal adenocarcinoma



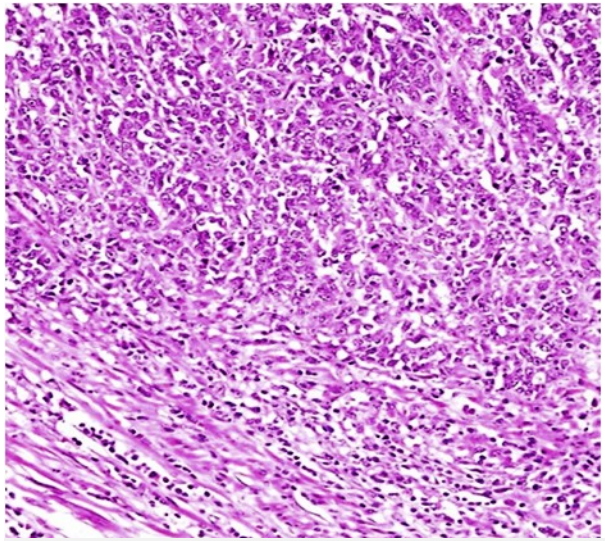
Adenocarcinoma NOS



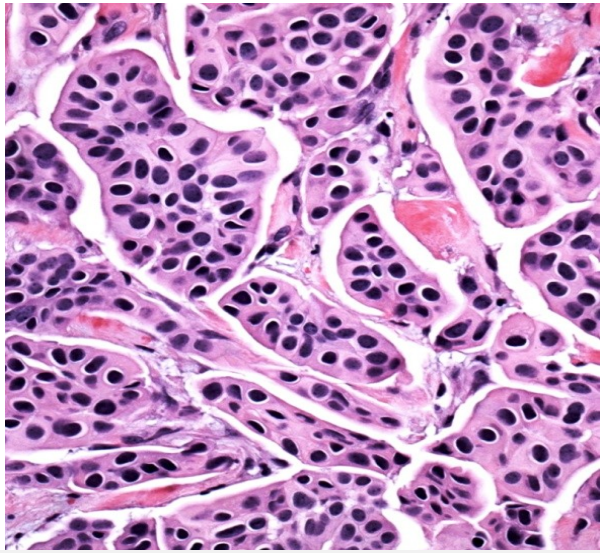
Mucinous



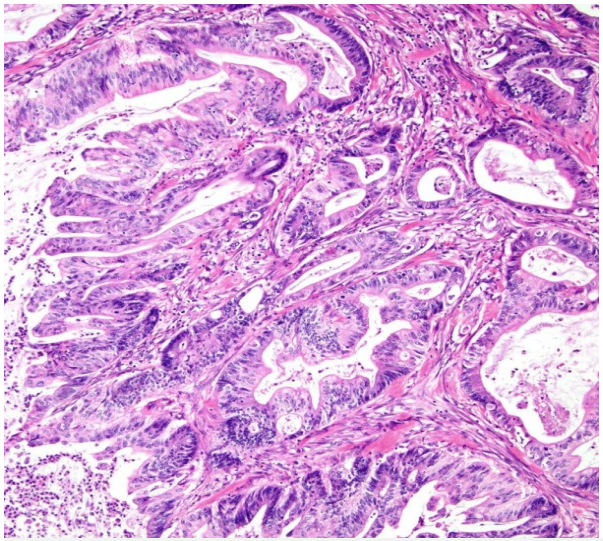
Signet ring cell



Medullary

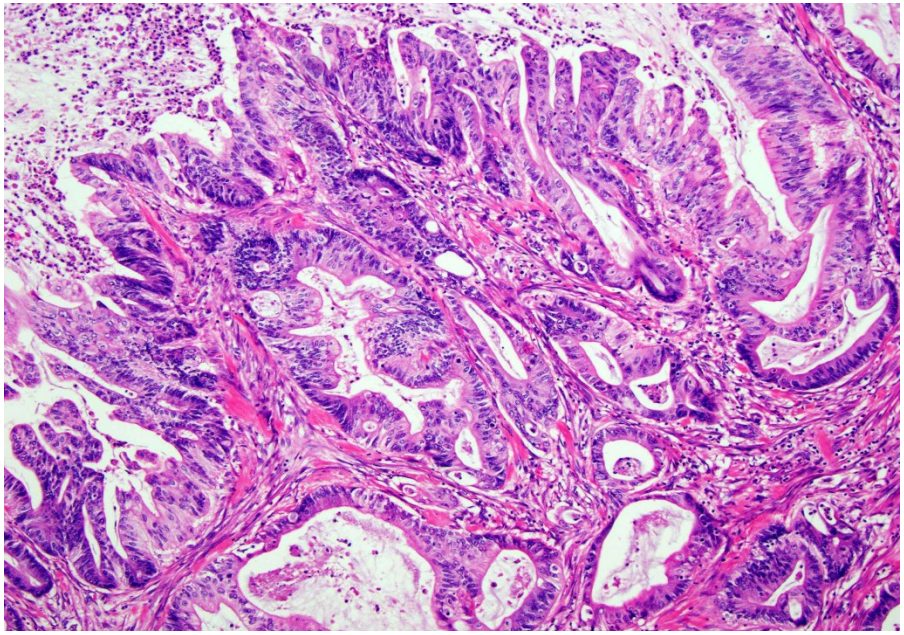


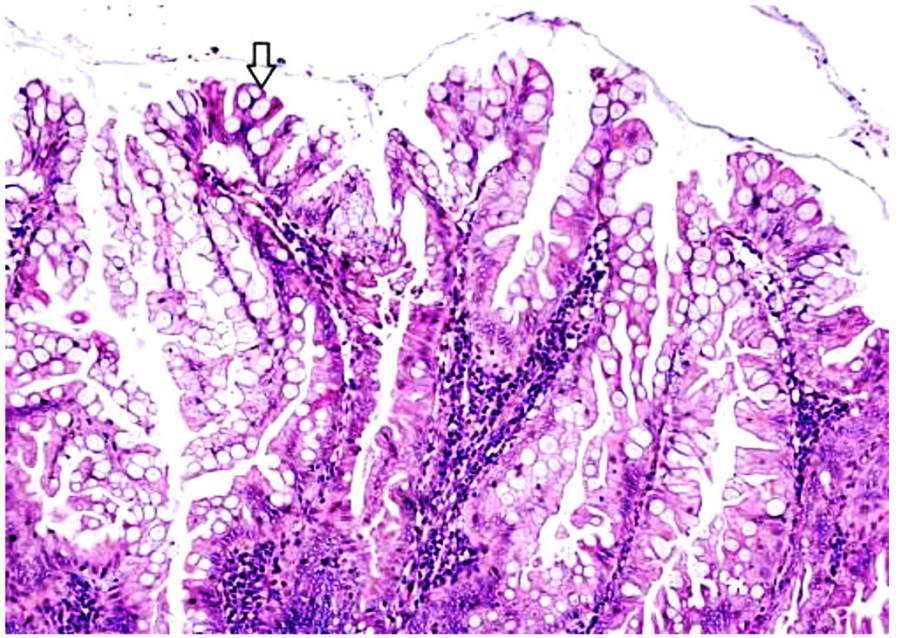
Micropapillary

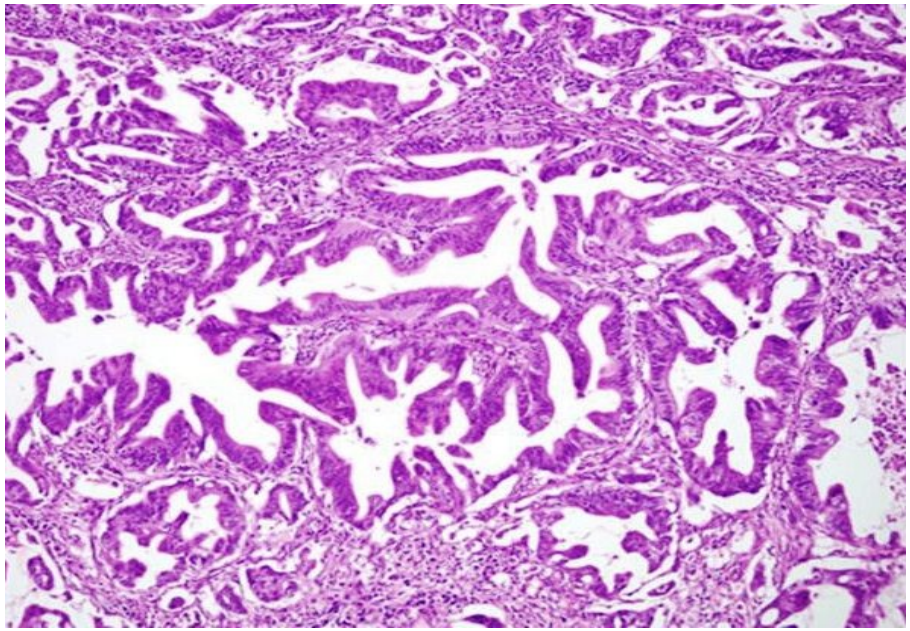


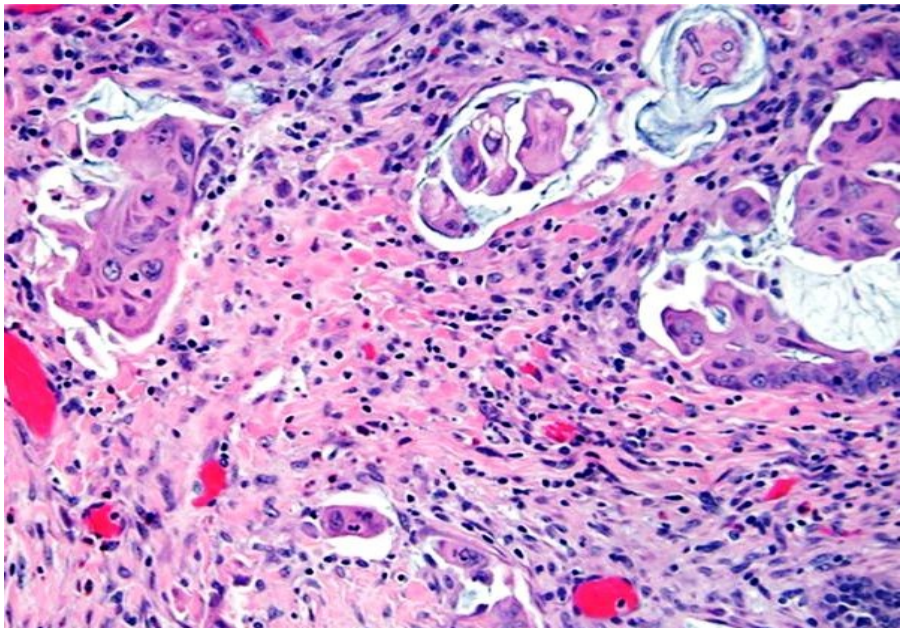
Serrated

Serrated adenocarcinomas of the colorectum









Prognostic factors in colorectal cancers (local, regional and distant factors)

Depth of invasion (Tumor Extent)

Tumours limited to the submucosa have 5-year survival rates of **95%** or more

Invasion of the muscularis propria reduces 5-year survival to **70%**

Serosal involvement reduces 5-year survival to **40%**

Lymph node metastases

Compromises survival to **30%** and cases with lymph node metastases **receive radiation or chemotherapy**

Distant metastases

Metastases to liver, lung, bone, brain, other sites **limit survival to 10%**

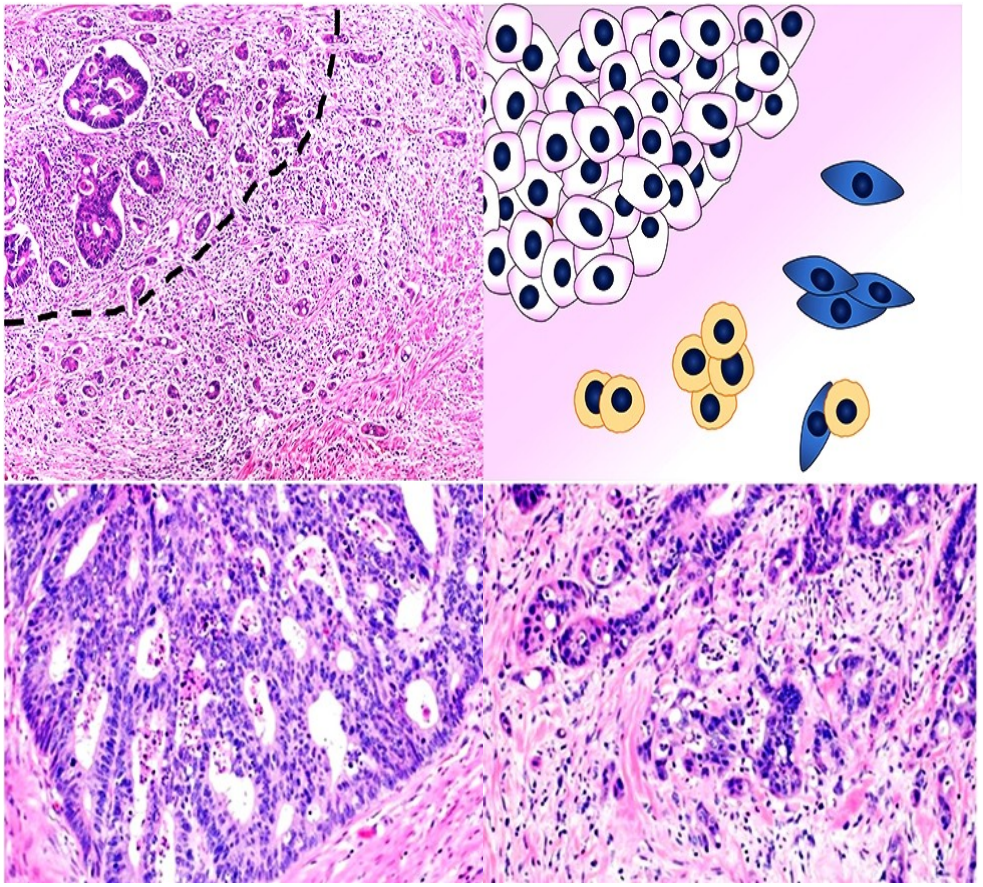
Tumour budding

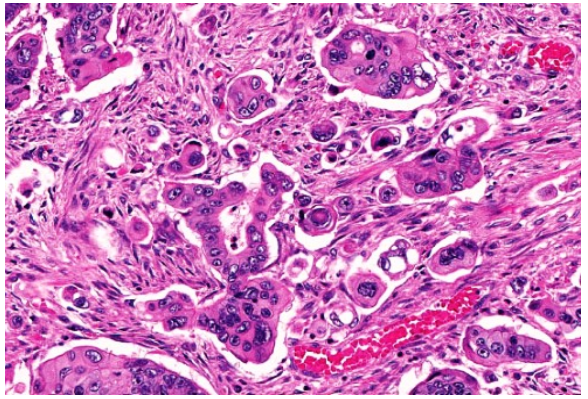
Tumour budding is defined as **single infiltrating cells or groups of up to 4 neoplastic cells** intimately associated with larger invasive glands

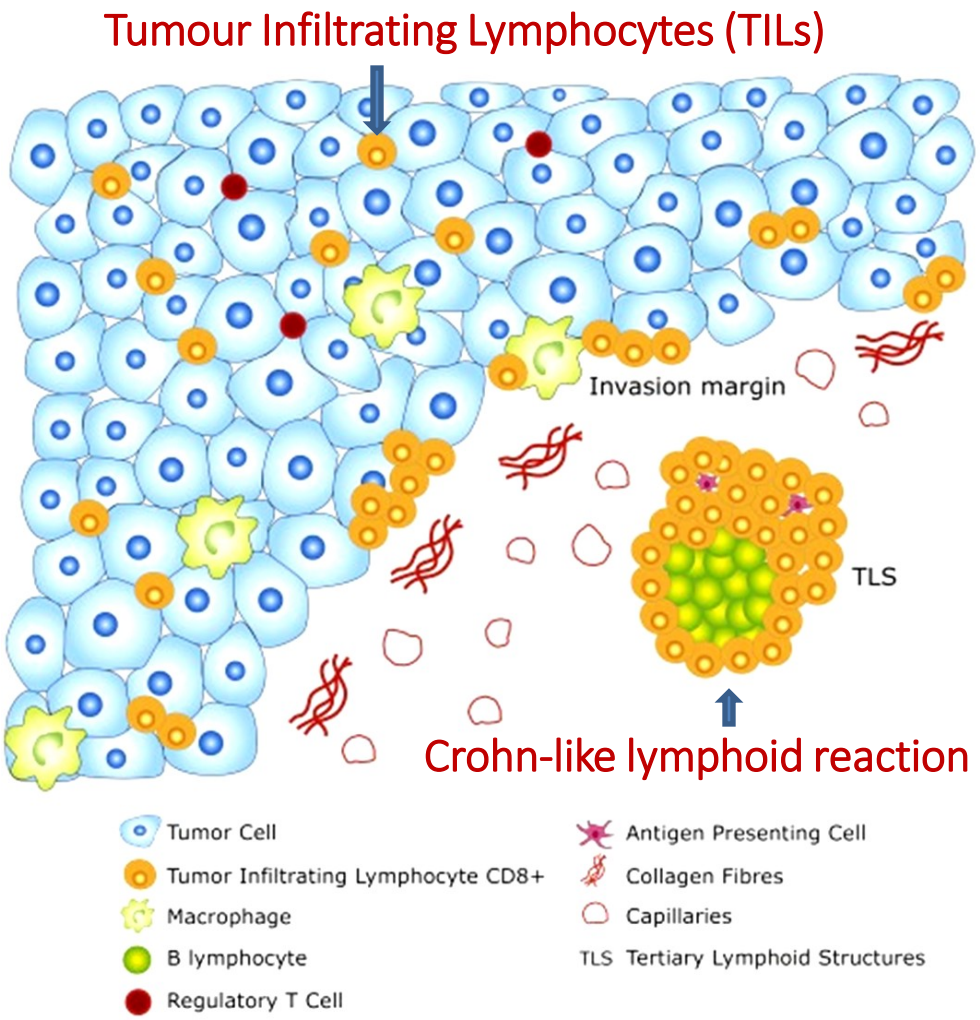
Tumor budding is **an independent prognostic factor, associated with tumor progression and adverse outcome**

Tumour budding is **graded** by assessing the number **of individual cells and small clusters per 20x** objective in **hot spots areas** (advancing tumour edge) as

- **Low (0-4 buds)**
- **Intermediate (5-9 buds)**
- **High (≥10 buds)**







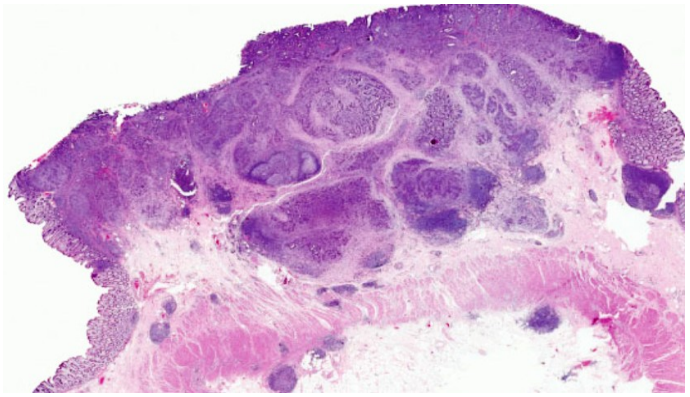
Host immune response

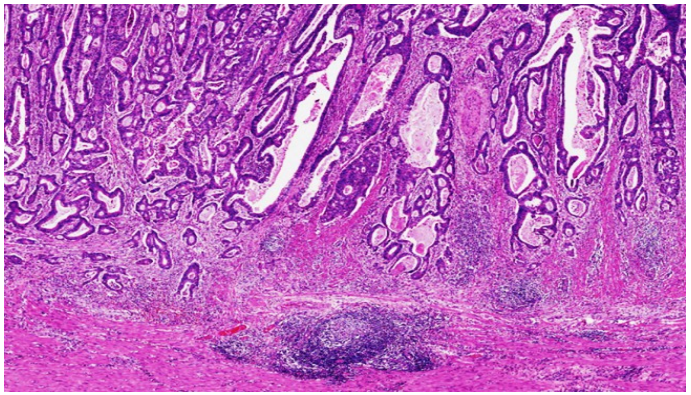
Independently associated with **improved outcome**, regardless of mismatch repair status

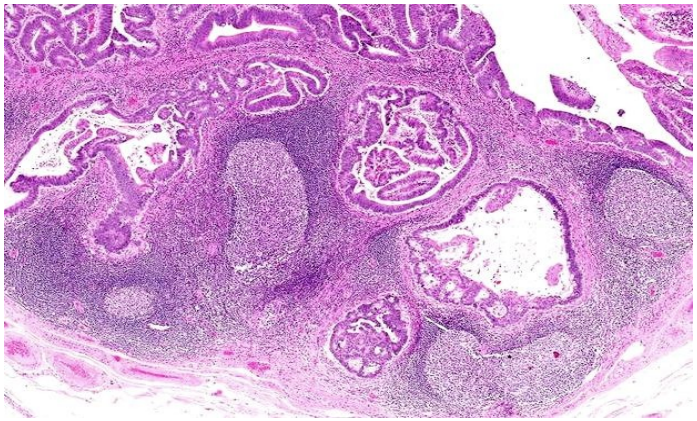
Crohn-like lymphoid reaction or tertiary lymphoid structure (TLS) (lymphoid follicles with germinal centres at the advancing tumour edge)

Tumour-infiltrating lymphocytes (TILs) with lymphocytes that directly oppose or surround tumor cells

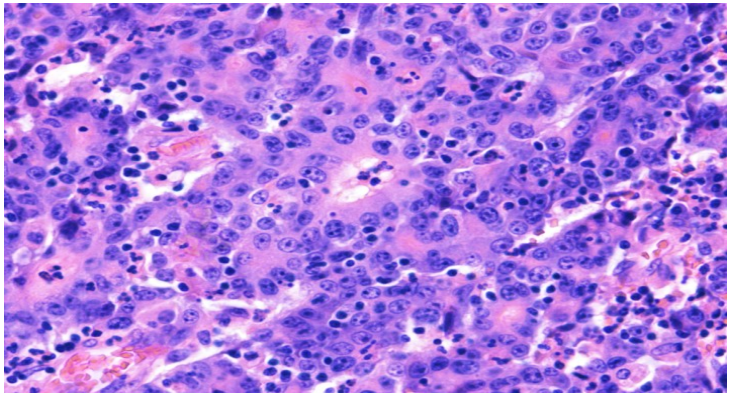
Crohn-like lymphoid reaction (CLR)

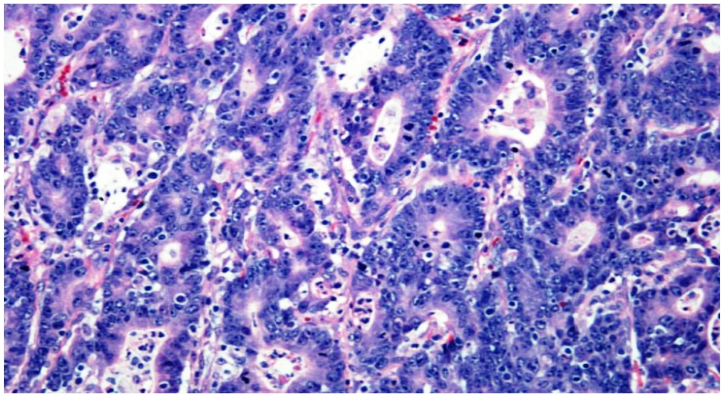


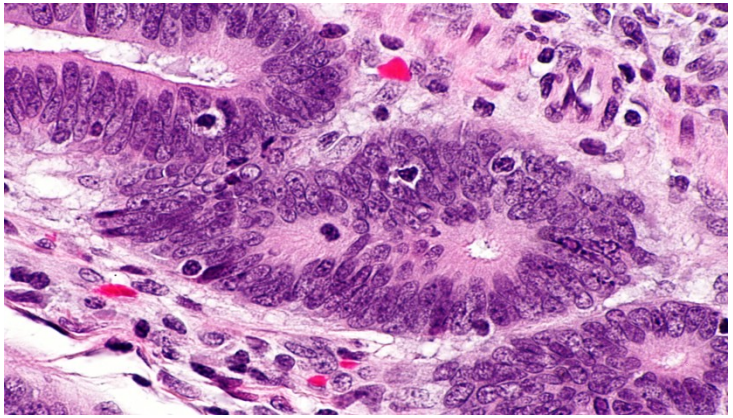




Tumor Infiltrating lymphocytes (TILs)

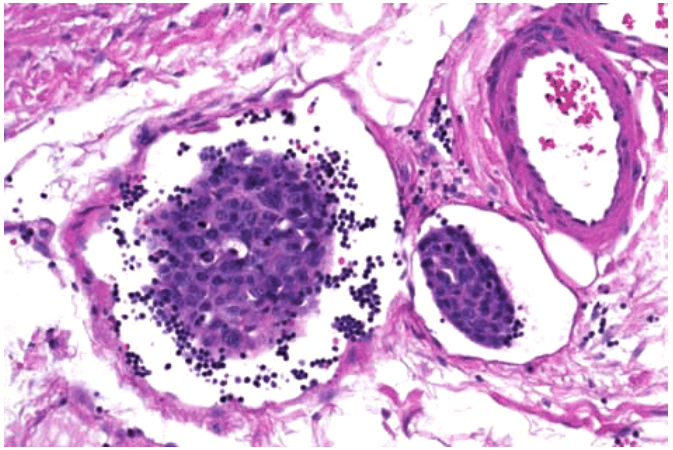




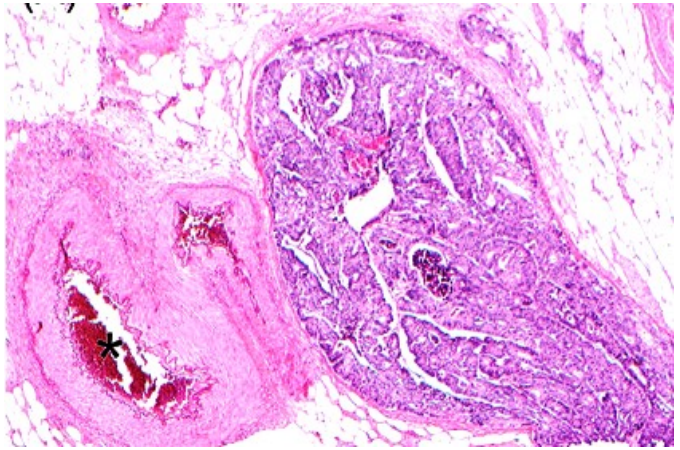


Prognostic features

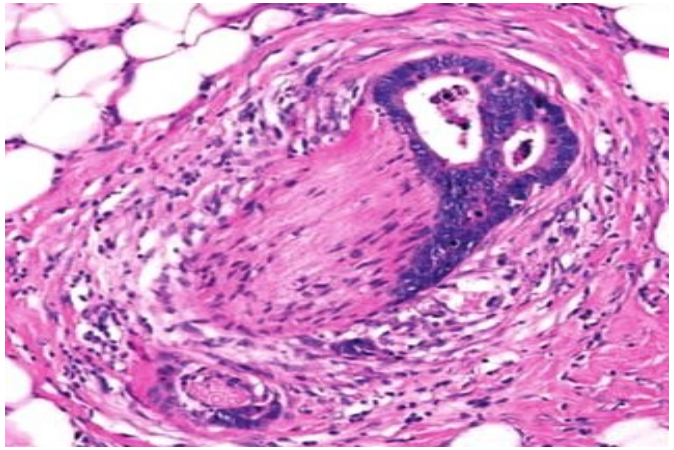
- Lymphovascular space invasion
  High predictive value for LN metastasis
  (60% vs 80%, 5 year survival)



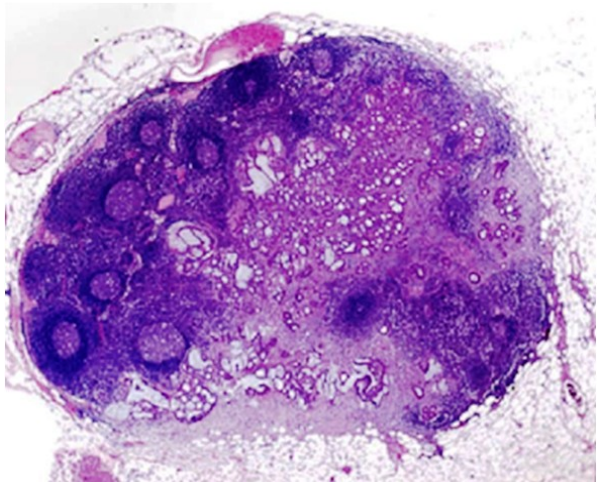
- Large vein invasion
  High predictive value for liver metastasis
  (40% vs 80%, 5 year survival)



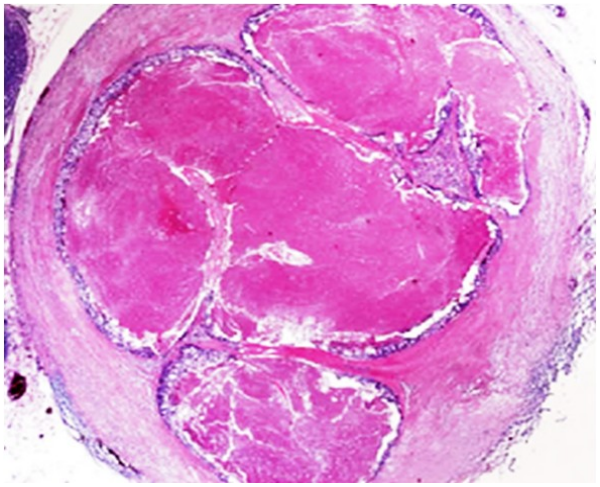
- Perineural Invasion
  High predictive value for LN and other tissues and distant spread
  (30% vs 80%, 5 year survival)

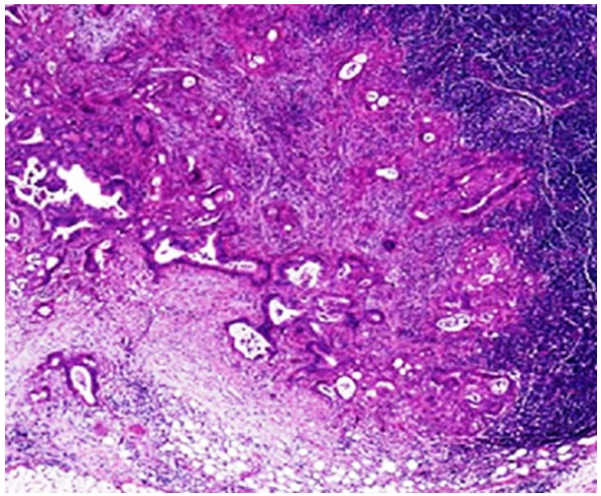


LN with metastatic carcinoma

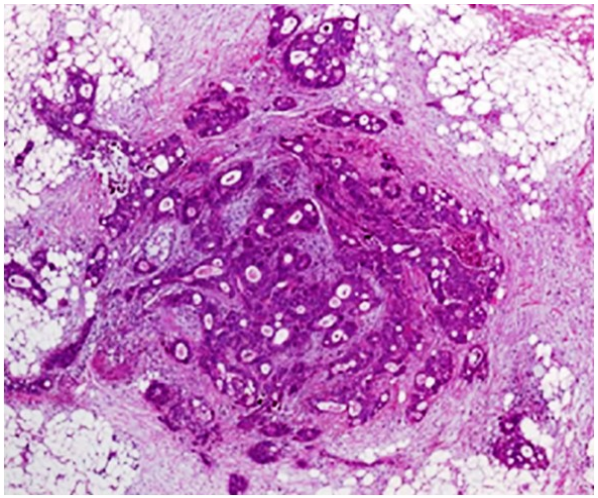


LN with metastatic carcinoma





LN with extranodal spread



Tumor deposit

Number of lymph node in resection specimens

Minimum of 12 LNs retrieved from the resection specimen is considered a quality indicator for adequate staging and oncological clearance

Fewer than 12 LNs even when all negative has been shown to correlate with **poorer prognosis,** particularly in stage II disease

Tumor deposit is **a discrete, discontinuous tumor nodules in pericolic or perirectal fat**, away from the primary tumor and lymph nodes, but within the lymphatic drainage area

Morphological pathways to cancer in the colorectum

Conventional pathway

Serrated pathway

Morphological Pathways to Colorectal Cancer

Morphology	Frequency	Examples	Molecular pathway TCAG
Conventional Pathway 1928	85%	Adenoma to carcinoma adenoma (tubular, tubulovillous, villous) Conventional morphology	Chromosomal instability (CIN) APC, KRAS, P53 mutation CIN +, CIMP -, MSS
Serrated Pathway 1996	15%	Serrated polyps to carcinoma (hyperplastic polyps, sessile serrated polyps, sessile serrated polyp with dysplasia) Traditional serrated adenoma Serrated morphology	BRAF mutation CIMP+, MSI CIMP+, MSS or MSI (MLH1 methylation) KRAS mutation

Pathways to Colorectal Cancer	
Conventional pathway	Serrated polyps pathway
Dysplastic epithelium with tubular, tubulovillous or villous growth pattern	Serrated epithelium Mostly non-dysplastic serrated or sawtooth growth pattern
Adenoma to carcinoma Tubular adenoma Tubulovillous adenoma Villous adenoma	Sessile serrated lesion with dysplasia to carcinoma Traditional serrated adenoma to carcinoma
Malignancy risk is high (10%)	Malignancy risk is low (1%)
Malignancy develops via the conventional pathway with APC, KRAS, p53 mutation (CIN)	Malignancy preceded by CIMP+, MSI or MSS with BRAF or KRAS gene mutations (Hypermutated)
Chromosomal instability (CIN)	Microsatellite instability (MSI) and CIM

CpG Island Methylator Phenotype (CIMP)

CIMP tumors, comprising 15% of colorectal cancers

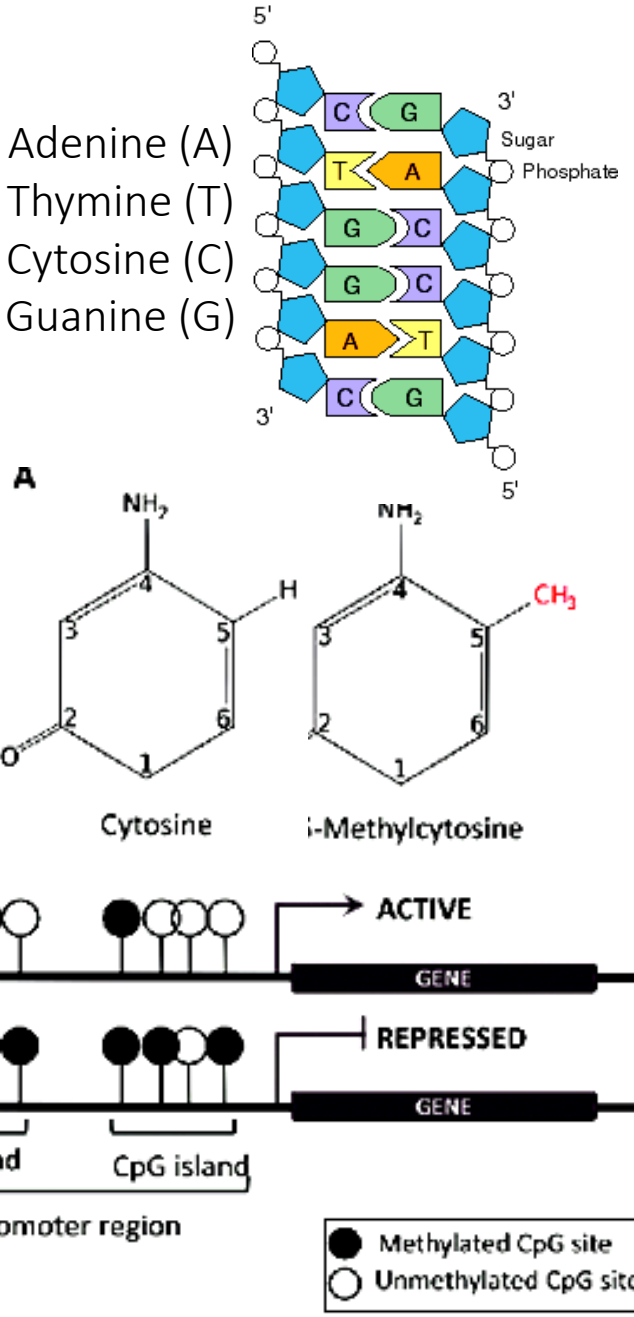
Associated with female sex, older age, right colon location, and BRAF mutations

CpG islands are **regions with high concentration of cytosine-guanine (C-G) pairs**

Found in many gene promoters regions

Normal CpG islands are **not methylated**

Methylation of CpG island can inactivate gene expression



Gene expression types in CRC

Chromosomal instability (CIN) - 70%

Inactivation of *APC*, KRAS and *TP53 mutations, CIMP-, MSI -*

Microsatellite instability (MSI) - 15%

Inactivation of DNA MMR genes, BRAF mutation

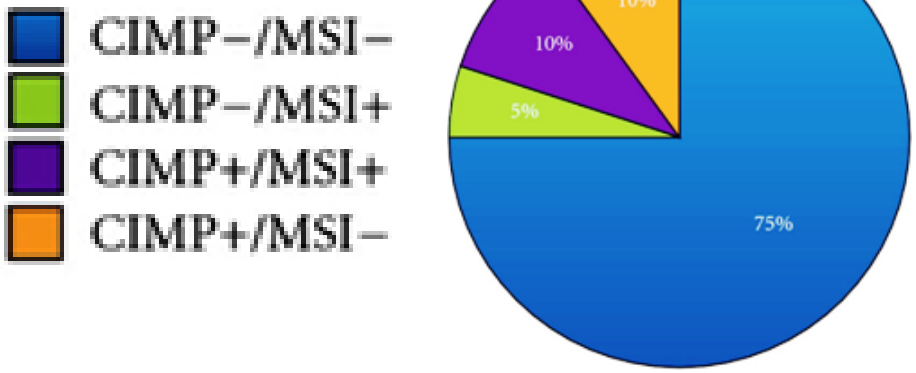
CpG island methylator phenotype (CIMP) - 15%

Hypermethylation of CpG island loci

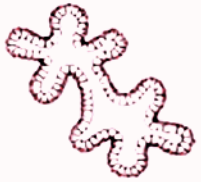
CIMP+ carcinomas develop from **sessile serrated polyps or traditional serrated adenomas**

CRC on the basis of both CIMP and MSI statuses:

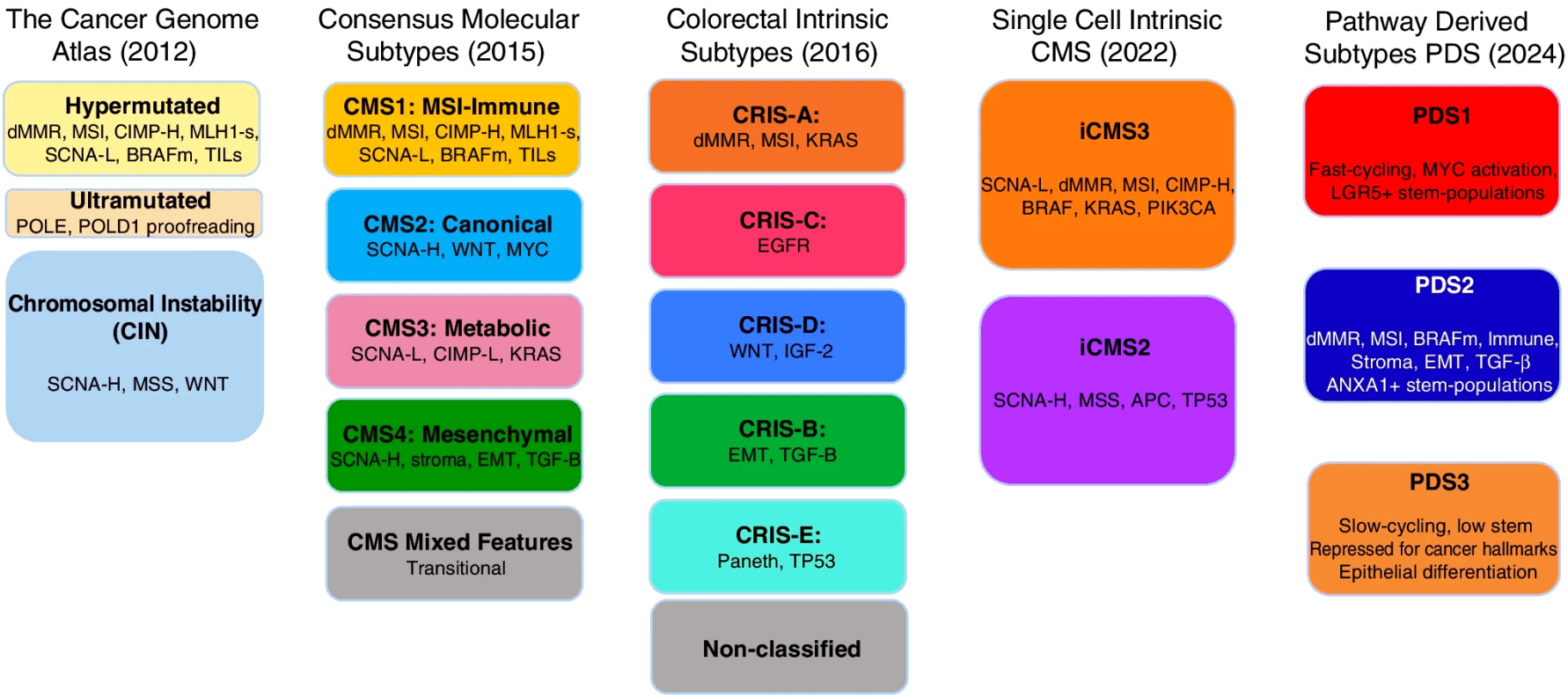
- CIMP−/MSI− (75%–80%)
- CIMP−/MSI+ (5%)
- CIMP+/MSI+ (10%)
- CIMP+/MSI− (5%–10%)

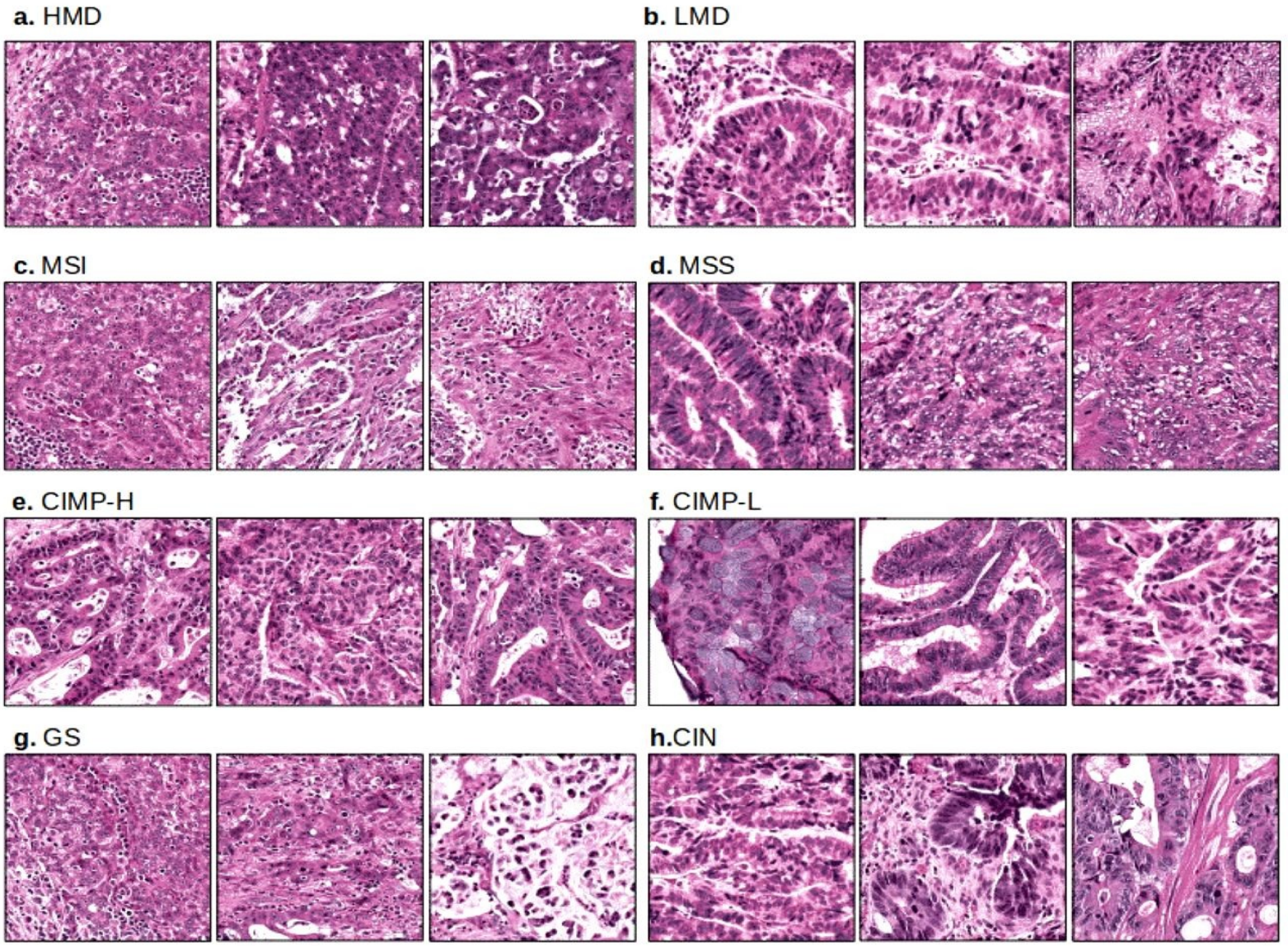


Consensus Molecular Subtype of CRC for better patient stratification, treatment selection and prognosis prediction (2015)

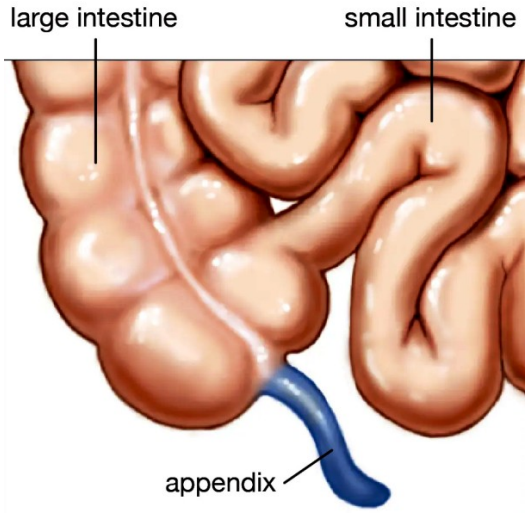
	CMS1	CMS2	CMS3	CMS4
Alternate Name	MSI immune	Canonical	Metabolic	Mesenchymal
Incidence	14%	37%	13%	23%
Molecular Features	MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
Mutations	*BRAF*		*KRAS*	
Signatures	Immune infiltration and activation	*WNT* and *MYC* activation	Metabolic deregulation	Stromal infiltration, *TGF-β* activation, angiogenesis
Clinical Features	Worse survival after relapse			Worse relapse-free and overall survival
Potential Precursor Lesions	 Serrated	Tubular adenoma	Uncertain (Tubulovillous adenoma with serrated features)	Serrated

SCNA = Somatic Copy Number Alteration; CIMP = CpG island methylator phenotype; TGFβ = Transforming Growth Factor β)


The Cancer Genome Atlas (2012)
Hypermutated
dMMR, MSI, CIMP-H, MLH1-s, SCNA-L, BRAFm, TILs
Ultramutated
POLE, POLD1 proofreading
Chromosomal Instability (CIN)
SCNA-H, MSS, WNT
Consensus Molecular Subtypes (2015)
CMS1: MSI-Immune
dMMR, MSI, CIMP-H, MLH1-s, SCNA-L, BRAFm, TILs
CMS2: Canonical
SCNA-H, WNT, MYC
CMS3: Metabolic
SCNA-L, CIMP-L, KRAS
CMS4: Mesenchymal
SCNA-H, stroma, EMT, TGF-B
CMS Mixed Features
Transitional
Colorectal Intrinsic Subtypes (2016)
CRIS-A:
dMMR, MSI, KRAS
CRIS-C:
EGFR
CRIS-D:
WNT, IGF-2
CRIS-B:
EMT, TGF-B
CRIS-E:
Paneth, TP53
Non-classified
Single Cell Intrinsic CMS (2022)
iCMS3
SCNA-L, dMMR, MSI, CIMP-H, BRAF, KRAS, PIK3CA
iCMS2
SCNA-H, MSS, APC, TP53
Pathway Derived Subtypes PDS (2024)
PDS1
Fast-cycling, MYC activation, LGR5+ stem-populations
PDS2
dMMR, MSI, BRAFm, Immune, Stroma, EMT, TGF-β ANXA1+ stem-populations
PDS3
Slow-cycling, low stem Repressed for cancer hallmarks Epithelial differentiation



Microsatellite instability (MSI), Chromosomal Instability (CIN), CpG Island Methylator Phenotype (CIMP), High Mutation Density (HMD), Genomically Stable (GS)



Appendiceal neoplasms

Mucinous Neoplasms

- Non-invasive
  - Low-grade appendiceal mucinous neoplasms (LAMN)
  - High-grade appendiceal mucinous neoplasm (HAMN)
- Invasive
  - Adenocarcinoma (Mucinous or non-mucinous)

Goblet cell adenocarcinoma (crypt cell carcinoma)

Neuroendocrine Neoplasms (NEN) and Mixed Neoplasms (MiNEN)

- Neuroendocrine Tumor (NET)
- Neuroendocrine Carcinoma (NEC)

Tumors of the appendix

Most common tumor is **neuroendocrine neoplasms (carcinoid)**

Other tumors include mucinous neoplasms (non-invasive and adenocarcinomas)

Tumors can cause luminal **obstruction** with distal enlargement

Tumors can **mimic acute appendicitis**

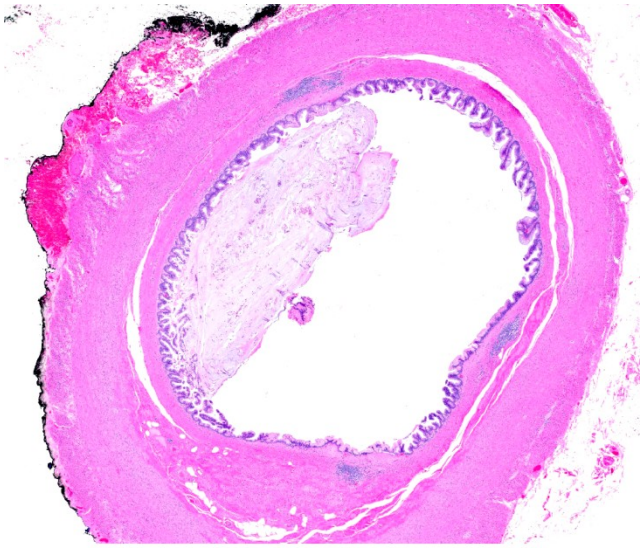
Tumors occur in **older patients**

Mucinous tumors without infiltrative invasion

Low-grade appendiceal mucinous neoplasm **(LAMN)**

High-grade appendiceal mucinous neoplasm **(HAMN)**

When confined to an intact appendix, patients are generally **cured by appendectomy**



LAMN

HAMN

Appendiceal mucinous neoplasms

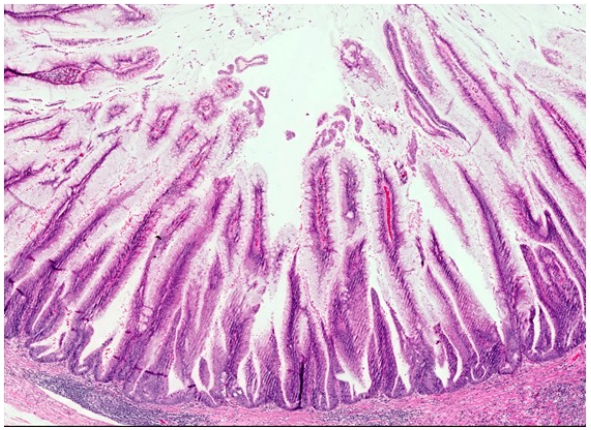
Replacement of appendiceal mucosa by **filiform (villous), undulating (scalloped), or flat mucinous epithelium.**

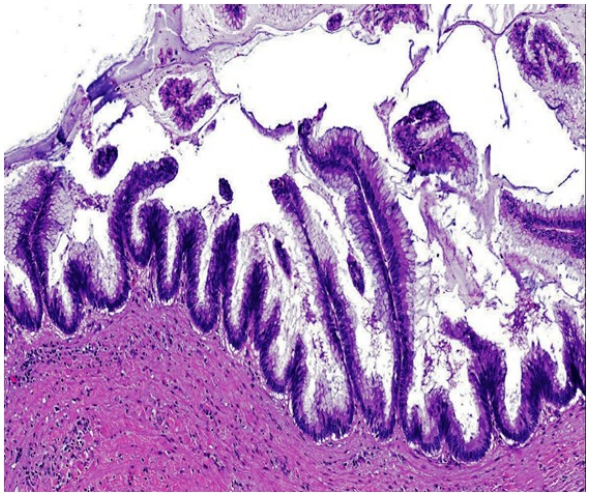
Tumour cells can be columnar with **cytoplasmic mucin vacuoles, pseudostratified or flat**

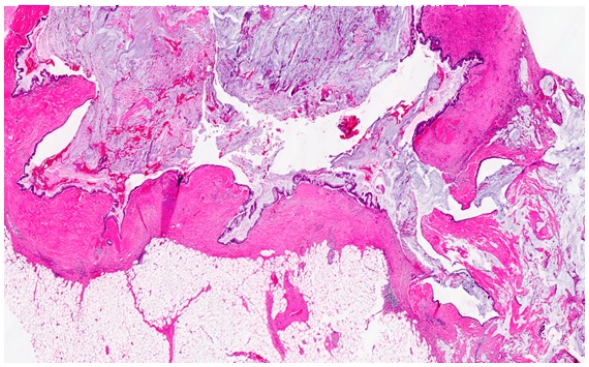
Tumour cells grow on **fibrotic submucosal tissue**.

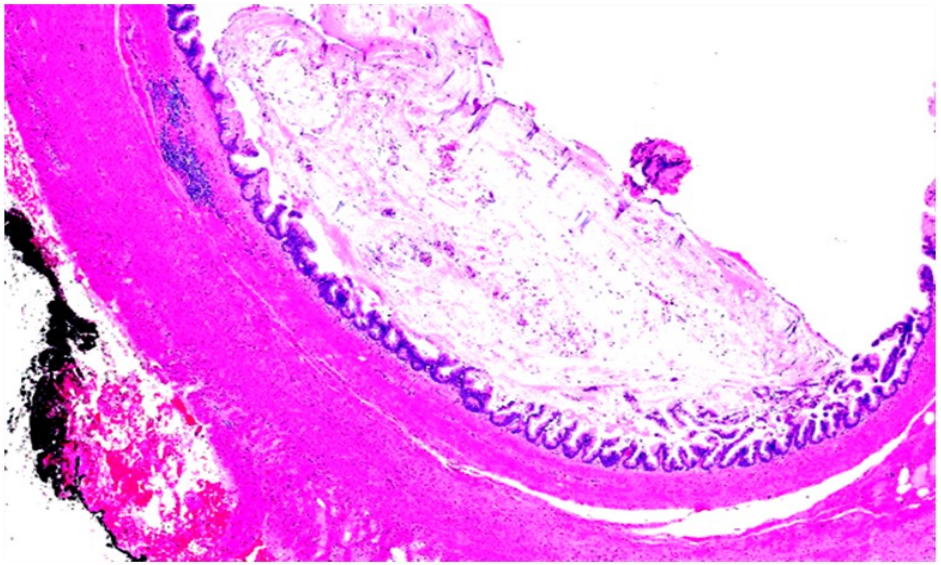
Nuclear atypia is mild in low grade (LAMIN) or marked in high grade (HAMIN)

Mucin can dissect through the appendiceal wall and extend to the peritoneal surface to cause **pseudomyxoma peritonei**

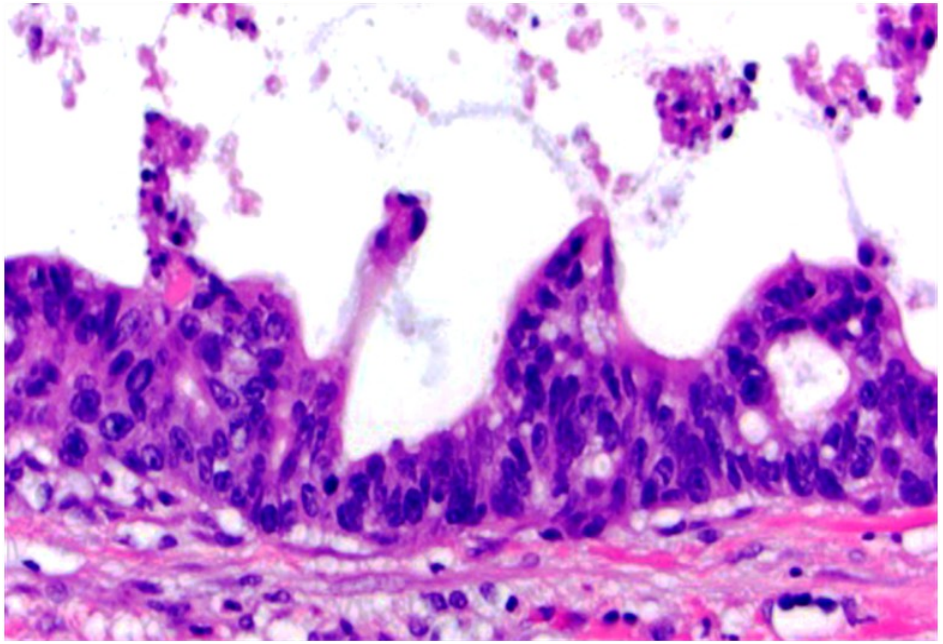








Low-grade appendiceal mucinous neoplasm (LAMN)



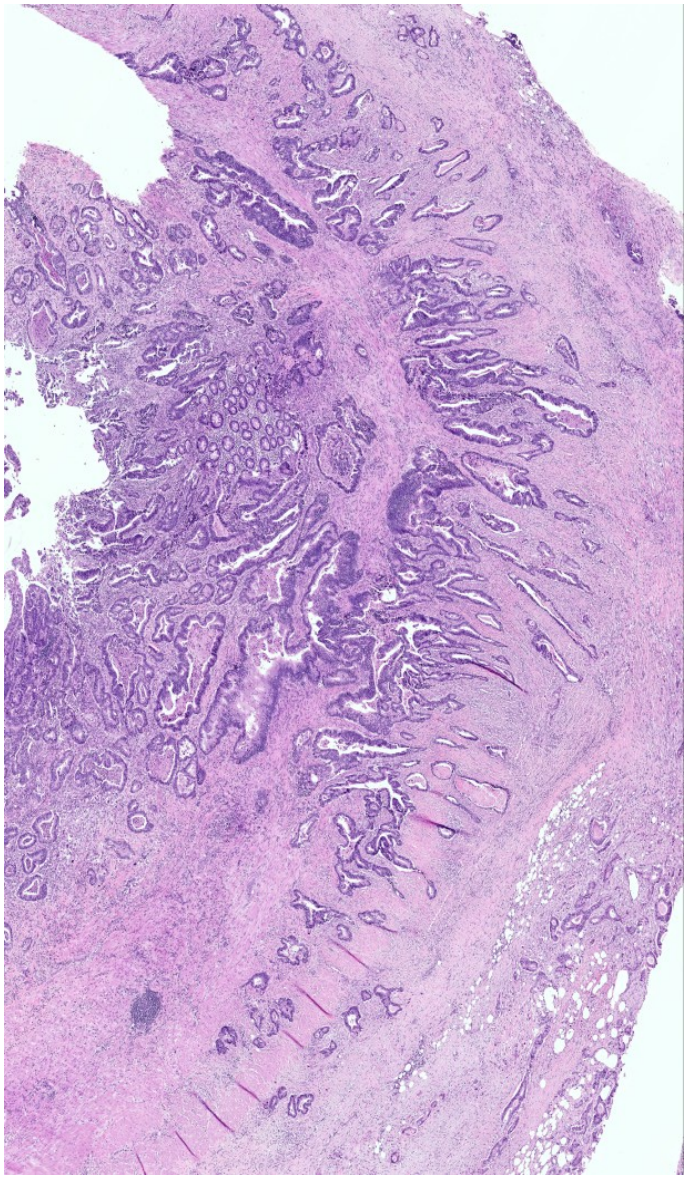
High-grade appendiceal mucinous neoplasm (HAMN)

Appendiceal adenocarcinomas

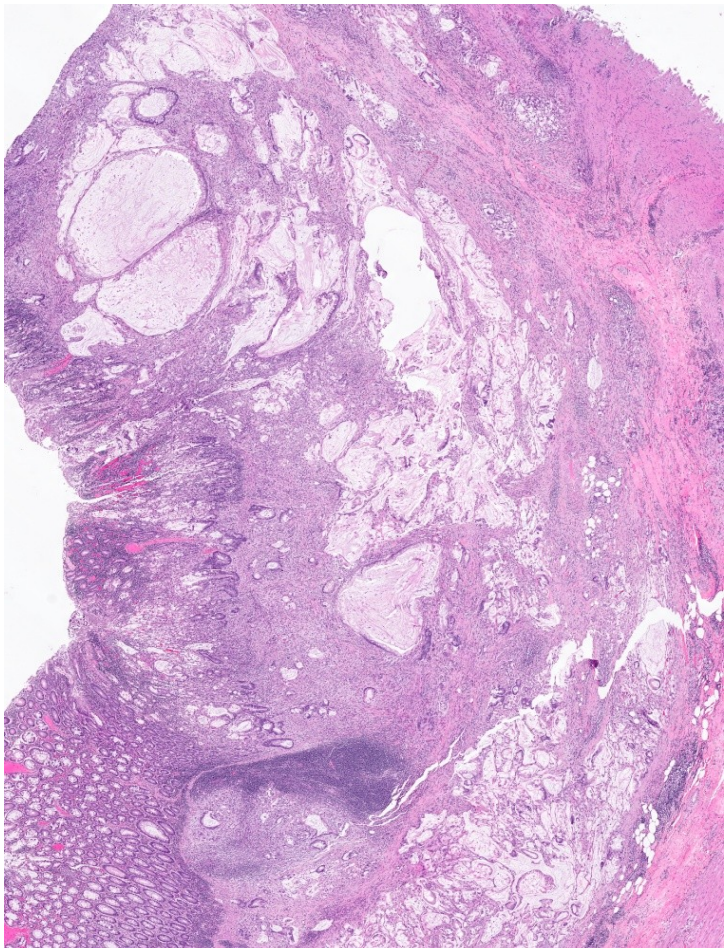
Resemble their colonic counterparts

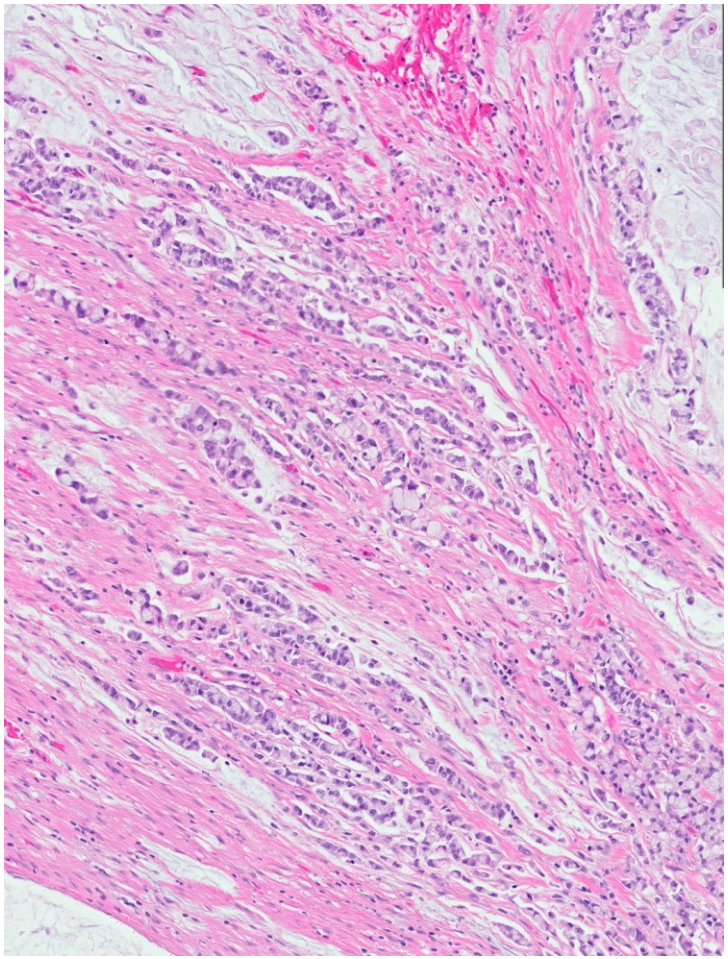
Intestinal-type, mucinous, or signet-ring cell differentiation.

Can cause **pseudomyxoma peritonei** (massive mucin accumulation in the peritoneal cavity, accompanied by omental caking and gelatinous serosal deposits)



Appendiceal adenocarcinoma

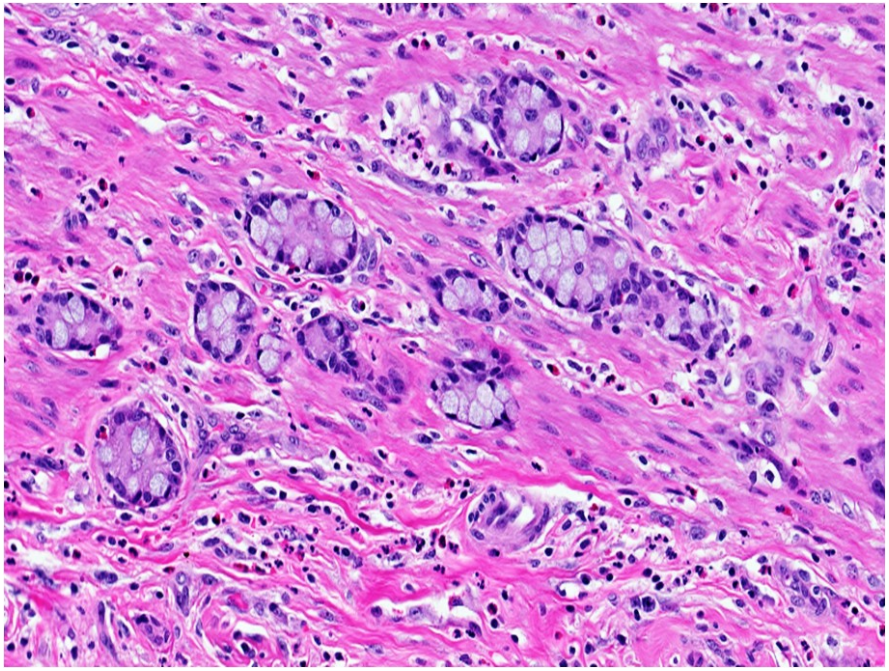


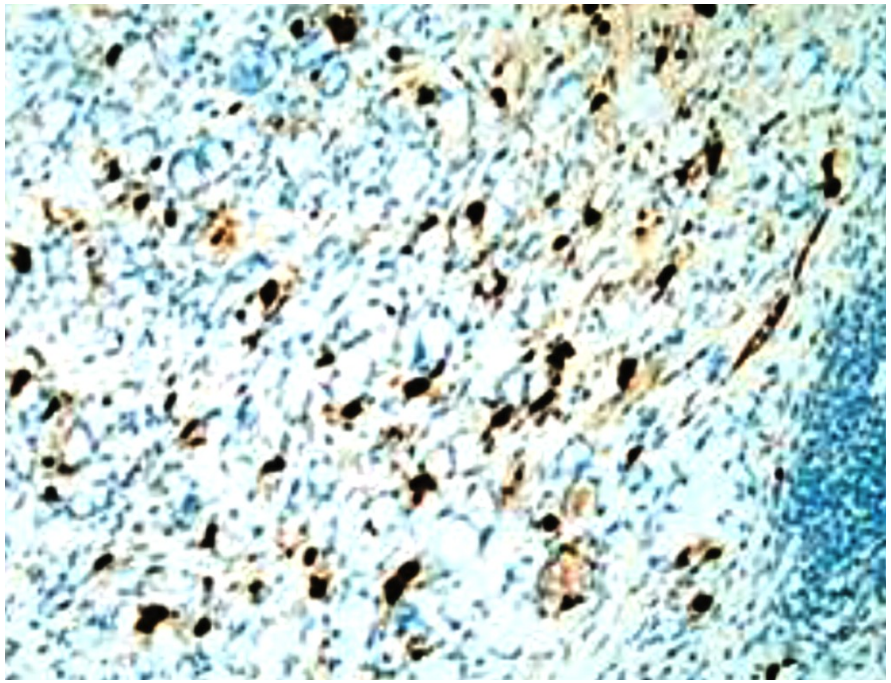


Goblet cell adenocarcinoma (crypt cell carcinoma)
Amphicrine (exocrine and endocrine) tumour

Composed of **mucinous cells** with **goblet cell morphology** and variable numbers of **endocrine cells and Paneth-like cells**

Tumour cells are typically arranged as **tubules resembling intestinal crypts**





Neuroendocrine neoplasms

Seen in **<1% of appendicectomy specimens**

More common among **adults**

Most tumors behave in a **benign manner.**

Majority are small tumors spanning **<2 cm**

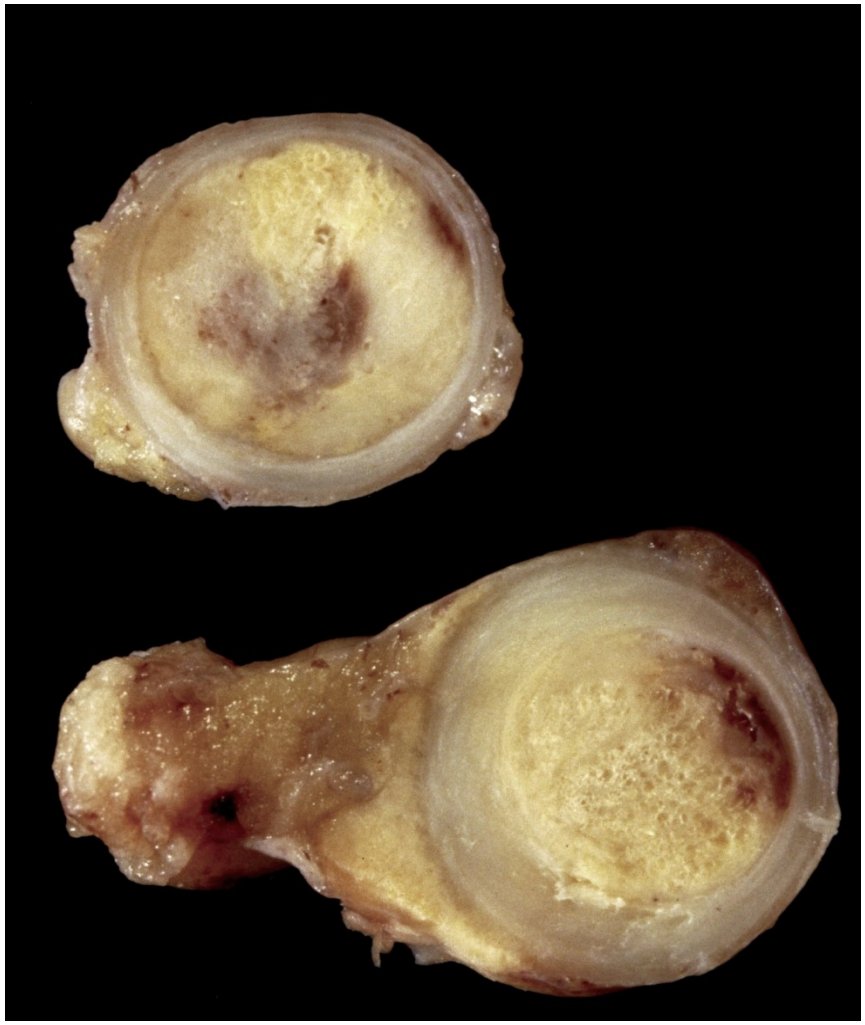
Tumors metastasize first to **regional lymph nodes followed by liver.**

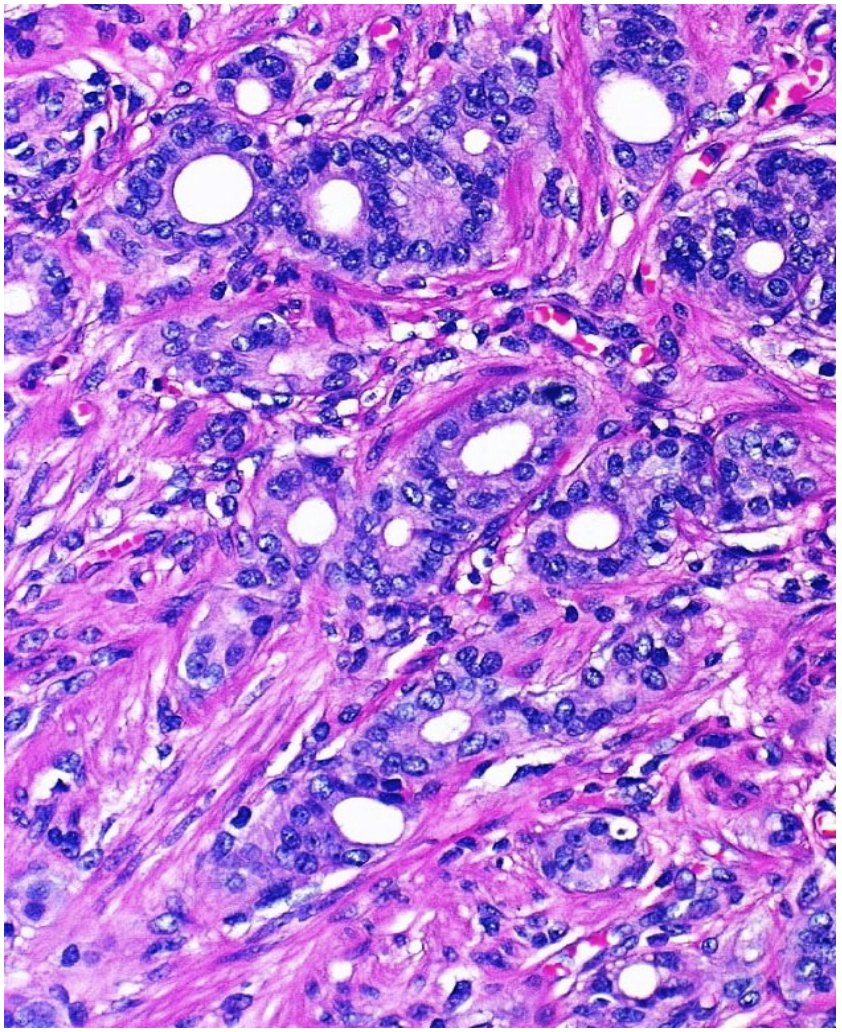
Small lesions up to 1 cm are generally treated with **appendectomy alone**

Right colectomy with lymph node dissection is considered when tumors are >2 cm

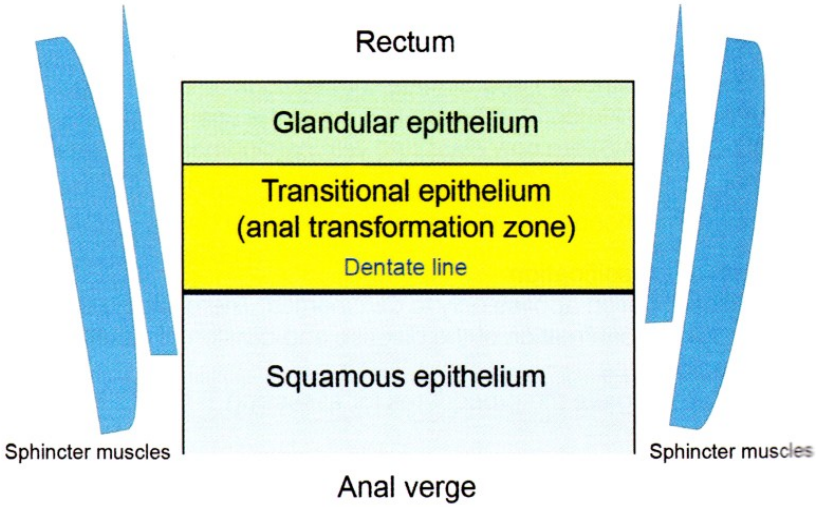
Tumor grading is assigned based on a combination of **mitotic activity and extent of Ki-67 staining.**

Neuroendocrine tumor





Anal Canal



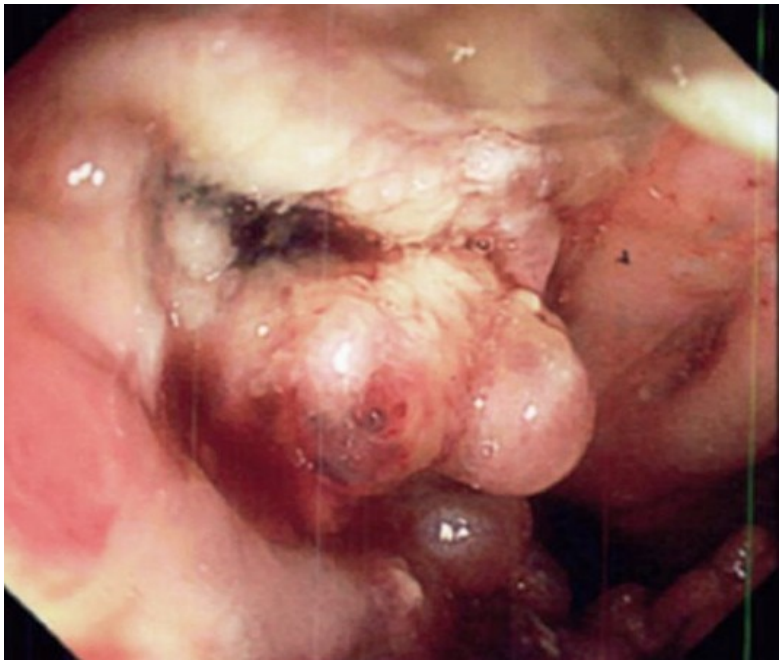
Epithelial tumors of the anal canal

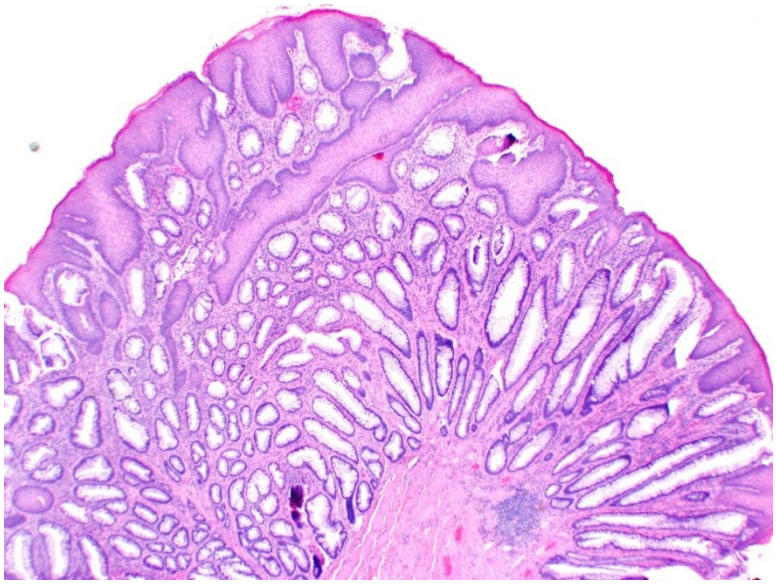
Benign epithelial tumours and precursors

- Inflammatory cloacogenic polyp
- Anal condyloma
- Anal squamous dysplasia (intraepithelial neoplasia)

Malignant epithelial tumours

- Anal squamous cell carcinoma
- Anal adenocarcinoma
- Anal neuroendocrine neoplasms





Inflammatory cloacogenic polyp (ICP)

Non-neoplastic polyp

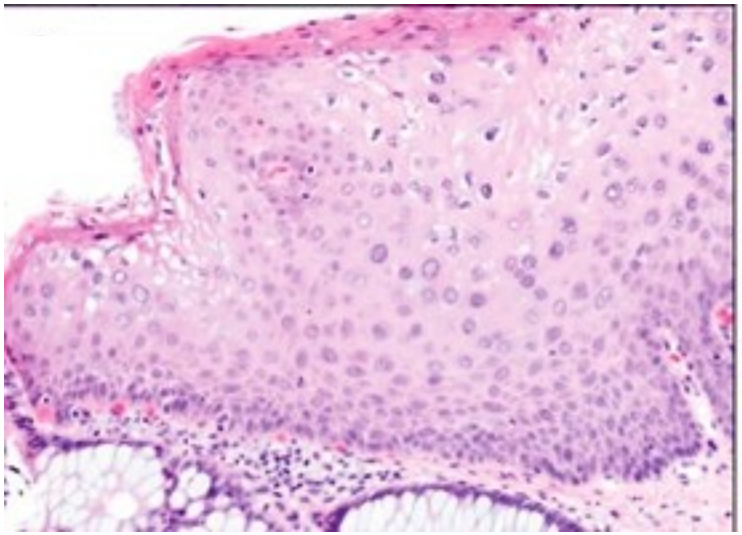
Arises in the **anal transitional zone**

Inflammation and glandular and smooth muscle proliferation

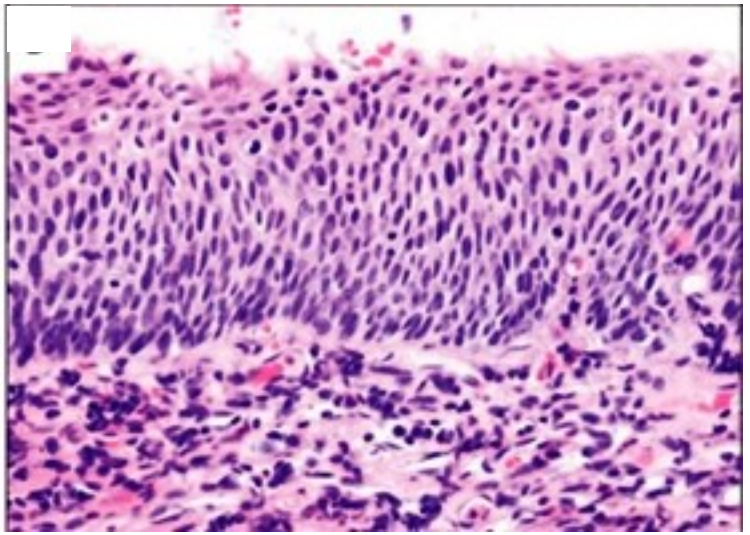
Related to a **low-fiber diet** (increase intraluminal colonic pressure) and similar to **mucosal prolapse polyp**

Does not recur after removal

Anal Squamous Dysplasia (Intraepithelial Neoplasia)	
Old Terminology	Lower Anogenital Squamous Terminology (LAST)
Mild dysplasia	Low Grade squamous Intraepithelial Lesion (LSIL)
Moderate dysplasia	High Grade squamous Intraepithelial Lesion (HSIL)
Severe dysplasia	High Grade squamous Intraepithelial Lesion (HSIL)
Carcinoma in situ	High Grade squamous Intraepithelial Lesion (HSIL)
Other Terminologies: AIN = Anal Intraepithelial Neoplasia; ASIN = Anal Squamous Intraepithelial Neoplasia	



LSIL



HSIL

Anal condyloma

Benign papillary squamous proliferation caused by **low risk HPV** subtypes HPV6 and HPV11

Buschke–Lowenstein tumor (BLT) is a giant condyloma with features of deep growth and local destruction

Condyloma occurs in the **anal canal, anal transformation zone, anal skin and perianal region**

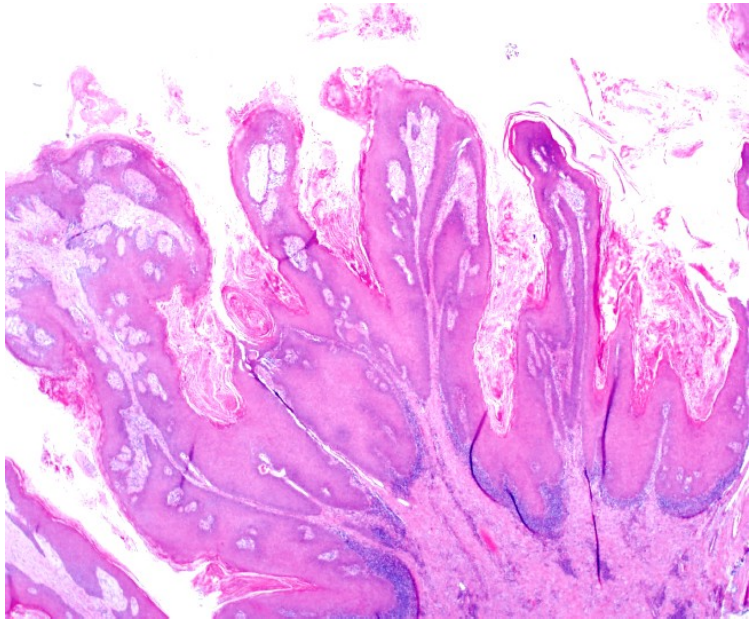
Anal condyloma

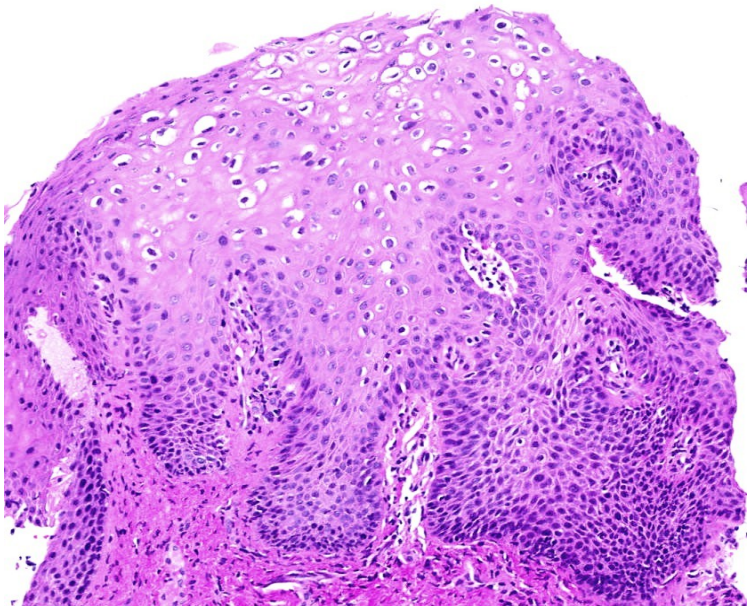
Squamous papilloma with **hyperplastic surface squamous epithelium with koilocytosis**

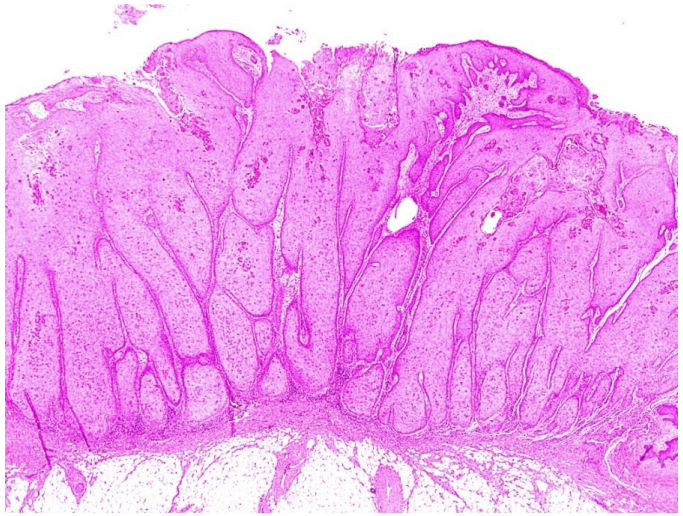
Large condyloma must be differentiated from verrucous carcinoma and BLT

Small condyloma can regress and be treated conservatively

Large condyloma and Buschke–Lowenstein tumor (BLT) do not regress spontaneously and are prone to recurrence and malignant transformation **(verrucous carcinoma)**



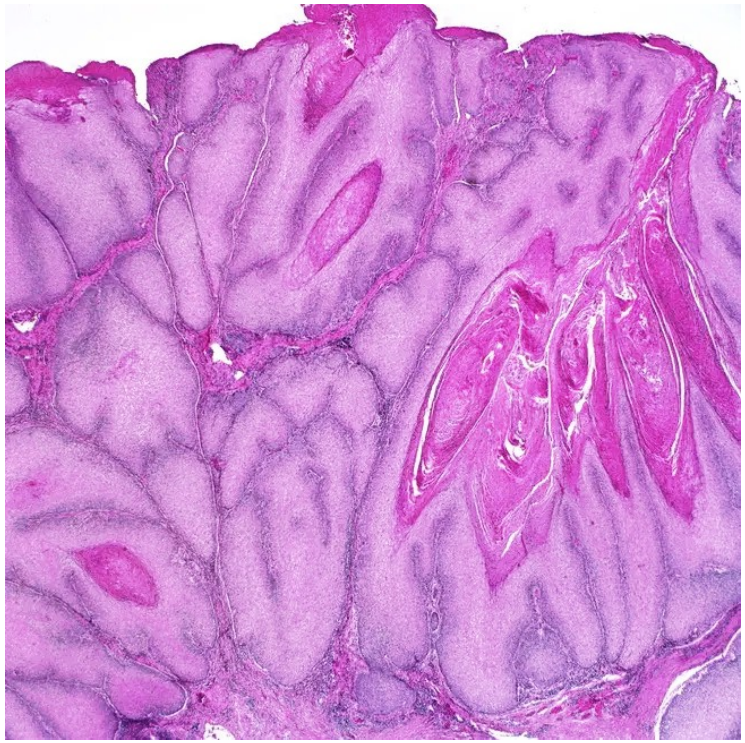




Verrucous Squamous Cell Carcinoma (VSCC)

VSCC is a **well-differentiated** variant of SCC primarily occurring in the **oral cavity, with additional sites including larynx, esophagus, anogenital region and sole of the foot**

Strong correlation with **tobacco and alcohol use** but relationship with **HPV,** though **both low-risk and high-risk types** have been **identified**



Verrucous Squamous Cell Carcinoma (VSCC)

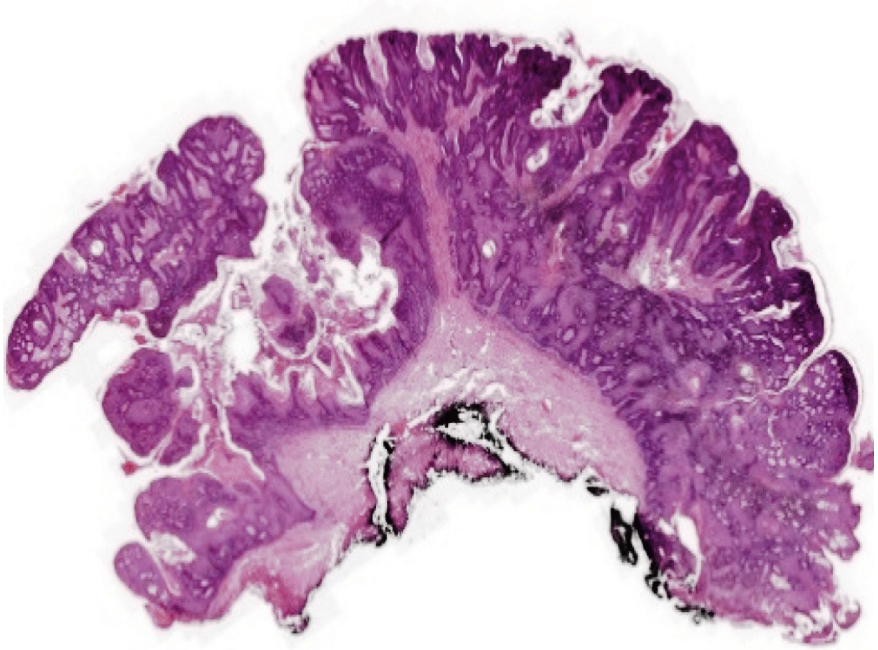
Present as **warty, cauliflower-like exophytic mass**

Well-differentiated SCC in large, rounded pushing nests with both exophytic and endophytic and endophytic growth patterns

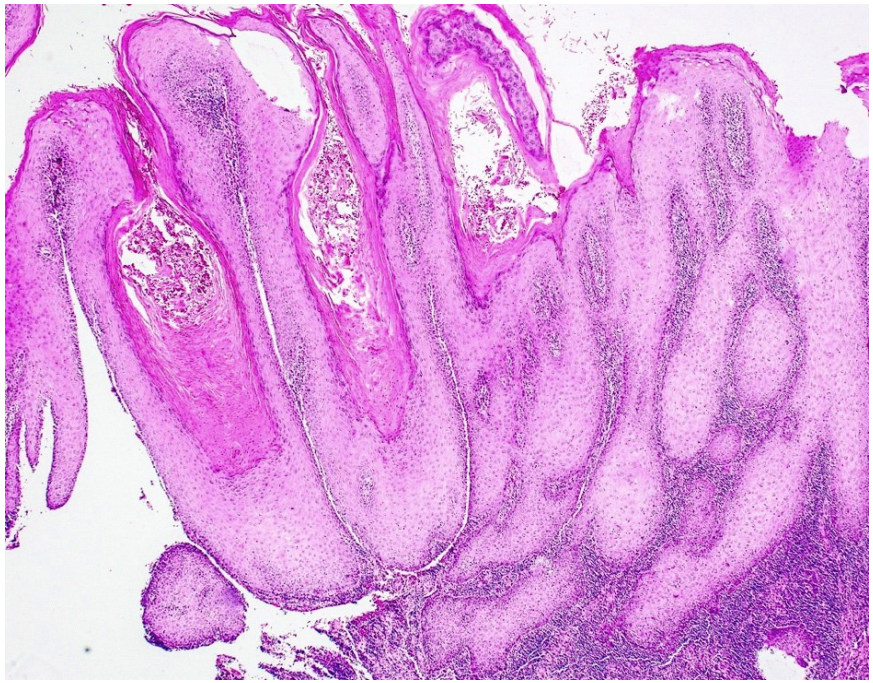
Tumour cells show abundant, 'glassy' eosinophilic cytoplasm with lacks cytological atypia.

Club-shaped or "elephant foot-like" projections with peripheral cup formation and Intact basement membrane are characteristic

Surface shows marked epithelial hyperplasia with filiform projections



Anal condyloma



Anal verrucous carcinoma

Anal adenocarcinoma

Arise in the **glandular epithelium** of the anal canal

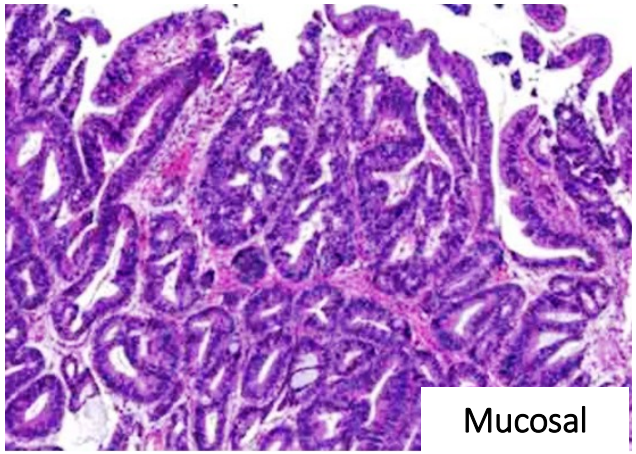
Two subtypes exist:

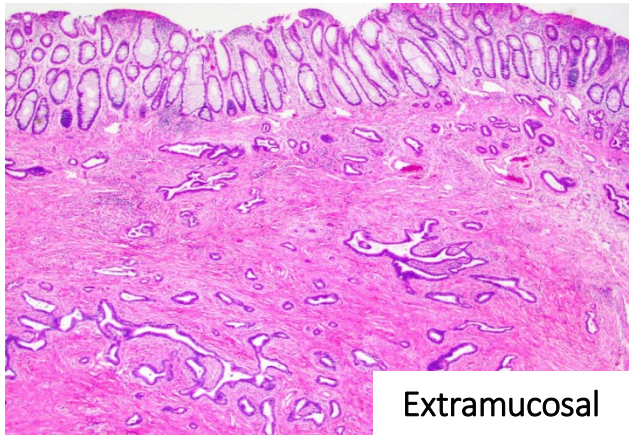
- **Mucosal**
- **Extramucosal**

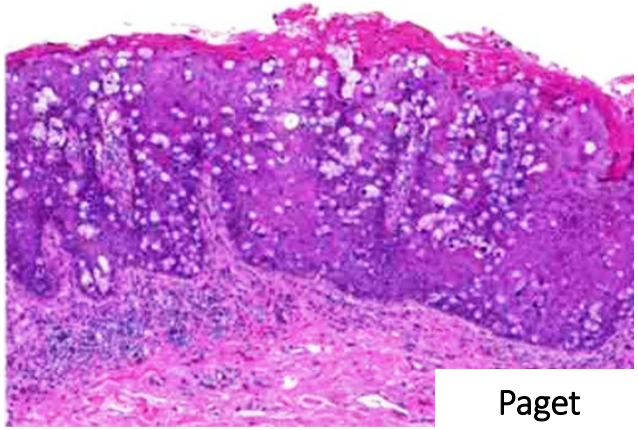
Mucosal ADC arises in the luminal mucosa and is of **intestinal type**

Extramucosal ADC may be associated with **anal gland, a pre-existing anal fistula or other non-fistulating glandular structures** of the anal canal (acquired or congenital malformations or embryological remnants)

May be of **anal gland type, mucinous type or intestinal type.**


Mucosal


Extramucosal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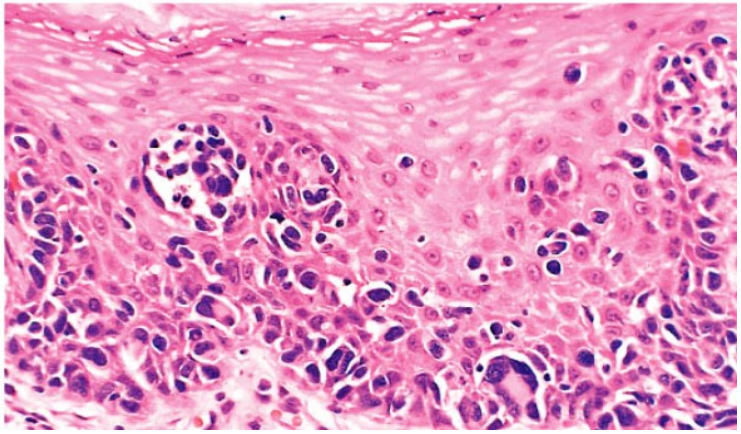
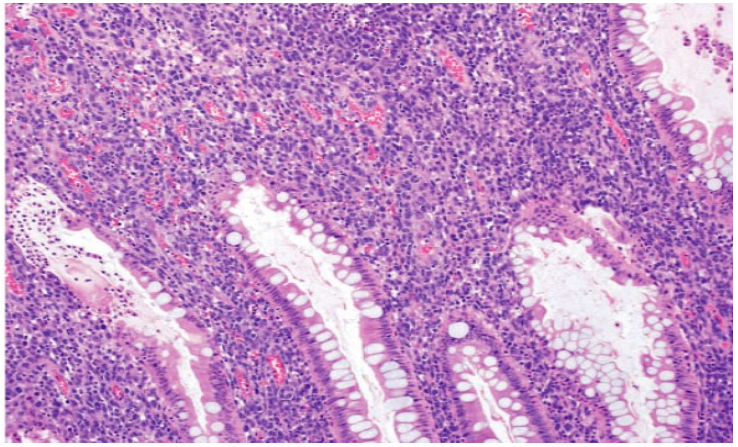
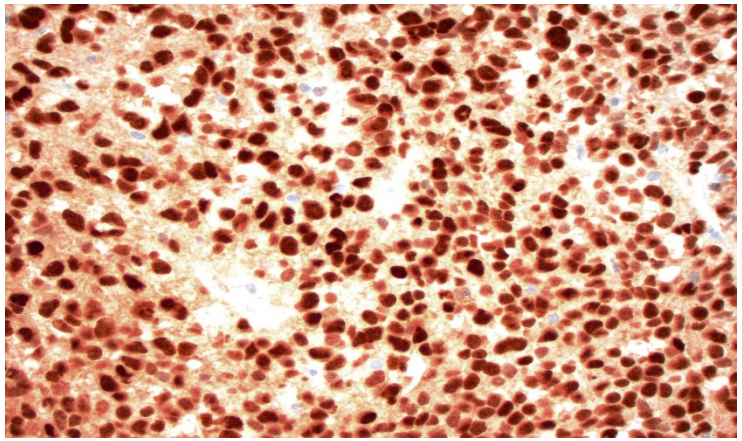






Anal melanomas (AMs)

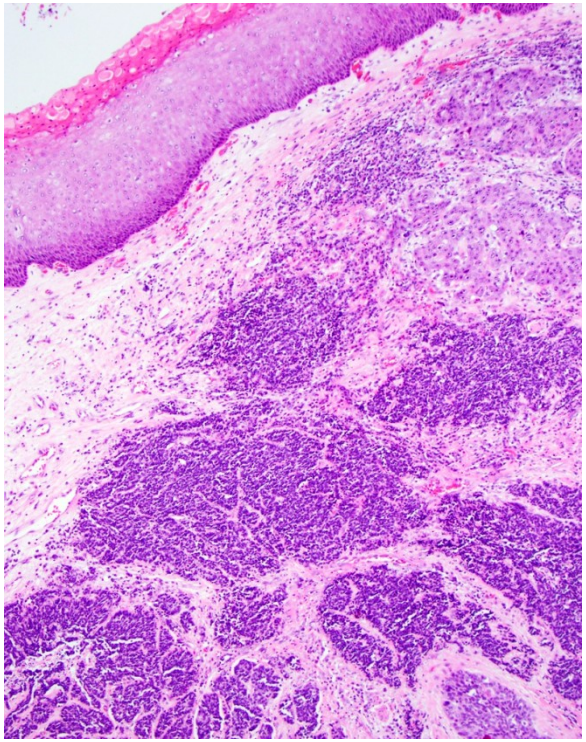
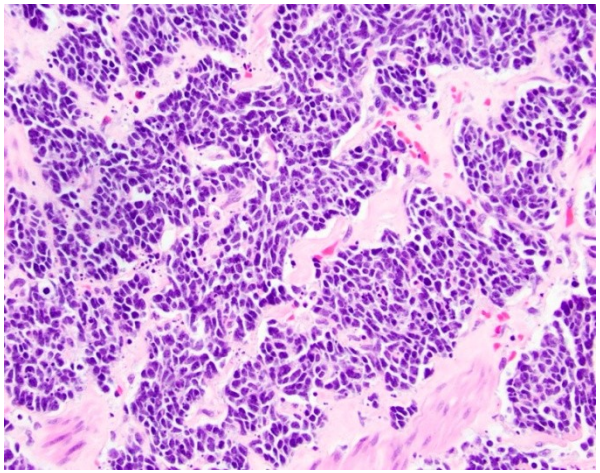
Account for about **1%** of all melanomas, usually present clinically with **bleeding, pain and mass** (same present as **hemorrhoids or anal polyps**)

Detected late in their course and are **advanced tumors** at the time of diagnosis

Frequently polypoid, possibly pigmented, and located at or adjacent to the **dentate line**

Same range of features and IHC reaction patterns as melanomas of the skin

Neuroendocrine neoplasms (NENs) of the anal canal

Anal epithelial neoplasms with neuroendocrine differentiation.

- Neuroendocrine tumour NOS
  - Neuroendocrine tumour, grade 1
  - Neuroendocrine tumour, grade 2
  - Neuroendocrine tumour, grade 3
- Neuroendocrine carcinoma NOS
  - Large cell neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
- Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)